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Health and Environmental Effects Profile for Formaldehyde

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The Health and Environmental Effects Profile for formaldehyde was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for formaldehyde.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for formaldehyde is 10.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR FORMALDEHYDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted dosage levels)
GC/MS	Gas chromatography/mass spectrometry
i.p.	Intraperitoneal
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MDI	Methylene di-para-phenylene isocyanate
MED	Minimum effective dose
NAD	Nicotinamide adenine dinucleotide
PMR	Proportional mortality ratio
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per thousand
RNA	Ribonucleic acid
RQ	Reportable quantity

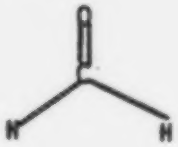
LIST OF ABBREVIATIONS (cont.)

SCE	Sister chromatid exchange
SMR	Standard mortality ratio
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Formaldehyde is the common chemical name, but it is also known by the synonyms methanal, oxymethane, methylene oxide, methyl aldehyde, oxymethylene and formic anhydride. The structure, molecular weight and empirical formula for formaldehyde are as follows:



Molecular weight: 30.03

Empirical formula: CH_2O

The CAS Registry number for formaldehyde is 50-00-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pure formaldehyde is a colorless gas with a pungent, suffocating odor at room temperature (Gerberich et al., 1980). Selected physical properties of pure formaldehyde are listed below:

Melting point:	-118°C	Gerberich et al., 1980
Boiling point:	-19°C (at 760 mm Hg)	Gerberich et al., 1980
Specific gravity:	0.815 (-20/4°C)	Verschueren, 1983
Vapor pressure at -88°C:	10 mm Hg	Verschueren, 1983
Heat of vaporization:	5.570 Kcal/g	Kitchens et al., 1976
Heat of combustion:	4.47 Kcal/g	Kitchens et al., 1976
Conversion factor (air):	1 mg/m^3 = 0.815 ppm	Verschueren, 1983
Log K_{ow}:	-0.65 (calculated) 0.00 (calculated)	Hansch and Leo, 1981 Verschueren, 1983

Formaldehyde gas is readily soluble in water, alcohols and other polar solvents at room temperature (Gerberich et al., 1980); however, formaldehyde solutions with these polar solvents are not true solutions, but are classified as solutions in which formaldehyde is in chemical combination with the solvent (Kitchens et al., 1976). Commercial formaldehyde is produced and sold as a water solution containing 37-50% formaldehyde by weight (commonly known as formalin), and may also contain a methanol inhibitor. These water solutions are complex equilibrium mixtures of methylene glycol, ($CH_2(OH)_2$), poly(oxymethylene glycols) and hemiformals of these glycols. Even in highly concentrated water solutions, the content of unhydrated formaldehyde is <0.04 wt.% (Gerberich et al., 1980).

Monomeric formaldehyde polymerizes readily, especially in the presence of impurities (Kitchens et al., 1976). It undergoes self-condensation to yield lower hydroxy aldehydes, hydroxy ketones and other hydroxy compounds (Gerberich et al., 1980). Formaldehyde reacts with many organic compounds to produce methylol or methylene derivatives (IARC, 1982).

1.3. PRODUCTION DATA

The commercial manufacturers, along with their respective locations and production capacities, are listed in Table 1-1.

Domestic production volumes of formaldehyde in recent years have been reported as follows (USITC, 1982, 1983, 1984):

Year	Production (millions of pounds; 37% by wt.)
1983	5464.9
1982	4816.5
1981	5720.7

Foreign trade of formaldehyde is negligible (Anonymous, 1984).

TABLE 1-1

Commercial United States Manufacturers of Formaldehyde[a]

Manufacturer	Location	Annual Capacity[b] (millions of pounds)
Borden Inc.	Demopolis, AL	95
	Diboll, TX	80
	Fayetteville, NC	235
	Fremont, CA	225
	Kent, WA	80
	La Grande, OR	65
	Louisville, KY	80
	Missoula, MT	90
	Sheboygan, WI	130
	Springfield, OR	240
	Geismar, LA	250
Celanese Corp.	Bishop, TX	1800
	Newark, NJ	117
	Rock Hill, SC	117
E.I. Du Pont de Nemours & Co., Inc.	Belle, WV	500
	Grasselli, NJ	160
	Healing Springs, NC	220
	La Porte, TX	320
	Toledo, OH	270
GAF Corp.	Calvert City, KY	100
	Texas City, TX	100
Georgia-Pacific Corp.	Albany, OR	120
	Columbus, OH	165
	Conway, NC	100
	Crossett, AK	165
	Lufkin, TX	100
	Russellville, SC	200
	Taylorsville, MS	120
	Vienna, GA	100
Getty Oil Co.	Andalusia AL	70
	Moncure, NC	120
	Springfield, OR	140
	Winnfield, LA	70
Hercules Inc.	Louisiana, MO	170

TABLE 1-1 (cont.)

Manufacturer	Location	Annual Capacity[b] (millions of pounds)
International Minerals & Chem. Corp.	Seiple, PA	135
Monsanto Co.	Addyston, OH	115
	Chocolate Bayou, TX	180
	Eugene, OR	100
	Springfield MA	295
	Fords, NJ	185
	Vicksburg, MS	54
Reichhold Chems., Inc.	Hampton, SC	50
	Houston, TX	110
	Kansas City, KS	50
	Tacoma, WA	32
	Tuscaloosa, AL	73
	White City, OR	200
	Acme, NC	80
	TOTAL	8573

[a] Source: SRI, 1984

[b] Capacities are on a 37% basis.

Formaldehyde is manufactured by the catalyzed air oxidation of methanol (Gerberich et al., 1980), resulting in an aqueous solution of formaldehyde as an end product.

1.4. USE DATA

Formaldehyde has the following use pattern (CMR, 1983):

urea-formaldehyde resins	27%
phenolic resins	21%
1,4-butanediol	9%
polyacetal resins	9%
pentaerythritol	7%
hexamine	7%
urea-formaldehyde concentrates	6%
melamine	4%
MDI	4%
other	6%

Formaldehyde is used predominantly as a chemical intermediate, but it does have minor uses as an end-product not involving chemical synthesis. These minor uses include the following: agriculture (seed treatment, soil disinfectant), analytical reagents, concrete and plaster additives, cosmetics (foot antiperspirants, deodorants, germicidal soaps), disinfectants and fumigants (in houses, barns, hospitals, etc.), embalming, leather tanning, metal corrosion inhibitor, photography and wood preservation (IARC, 1982; Kitchens et al., 1976). Until being banned in 1982 by the U.S. Consumer Product Safety Commission, formaldehyde as urea formaldehyde foam was extensively used as an insulating material (Federal Register, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of formaldehyde in the environment depends upon the ability of the compound to undergo chemical, photochemical and biological reactions and to transport or partition from one environmental matrix into another.

2.1. WATER

2.1.1. Hydrolysis. When formaldehyde gas is dissolved in aqueous solution, it is hydrated very rapidly; the first-order rate constant for the reaction of unhydrated formaldehyde with water is 9.8 sec^{-1} (Gerberich et al., 1980). In general, aldehydes are resistant to environmental hydrolysis (Lyman et al., 1982). Therefore, hydrated formaldehyde, which has the general formula $CH_2(OH)_2$, is not expected to undergo environmental hydrolysis.

2.1.2. Oxidation. Hydrated formaldehyde in aqueous solution is oxidized by hydroxyl radicals (•OH) as shown by the following reaction (Chameides and Davis, 1983):

$$CH_2(OH)_2 + \cdot OH \rightarrow CH(OH)_2 + H_2O$$

The rate constant for this reaction at room temperature is $2x10^9$ M^{-1} sec^{-1} (Chameides and Davis, 1983; Anbar and Neta, 1967; Dorfman and Adams, 1973); assuming an average •OH concentration of 10^{-17} M in aquatic media, a half-life of ~400 days can be calculated.

Additional data regarding the aqueous oxidation of formaldehyde were not located in the available literature as cited in the Appendix.

2.1.3. Photolysis. Experimental data regarding the aqueous photolysis of formaldehyde were not located. Gaseous formaldehyde undergoes rapid photolysis in the atmosphere (Section 2.2.); however, hydrated formaldehyde is not a chromophore and thus should not decompose photolytically under environmental conditions (Chameides and Davis, 1983). The potential for the photosensitized photolysis of hydrated formaldehyde in aquatic media is not known.

2.1.4. Microbial Degradation. Formaldehyde released to the aquatic environment appears to be susceptible to relatively rapid biodegradation. Kamata (1966) examined the biodegradation of formaldehyde in natural water obtained from a stagnant lake in Japan. Under aerobic conditions, known quantities of added formaldehyde were decomposed in ~30 hours at 20°C; anaerobic decomposition required ~48 hours. No decomposition was noted in sterilized lake water.

Various activated sludges and microorganisms isolated from activated sludges have been shown to be very efficient in degrading formaldehyde in aqueous effluents. Essentially complete degradation is achieved in 48-72 hours if the proper temperature and nutrient conditions are maintained (Kitchens et al., 1976). Grabinska-Loniewska (1974a,b) isolated 44 bacteria strains from an industrial activated sludge and found that formaldehyde was used as a sole carbon source by various Pseudomonas strains but not by strains of Achromobacter, Flavobacterium, Mycobacterium or Xanthomonas. Several studies have found significant degradation of formaldehyde by mixed cultures obtained from sludges and settled sewage (Behrens and Hannes, 1984; Sakagami and Yokoyama, 1980; Hatfield, 1957; Heukelekian and Rand, 1955; Speece, 1983), while other studies have found little or no degradation (Belly and Goodhue, 1976; Gerhold and Malaney, 1966; Chou et al., 1979; Placak and Ruchhoft, 1947; Kalmykova and Rogovskaya, 1978).

A number of pure culture studies have shown that formaldehyde is biologically degradable. Cell extracts of *Pseudomonas methanica* and *Methylosinus trichosporium* (Patel et al., 1979) and cell-free extracts of yeast strains of the *Candida* sp. are able to oxidize formaldehyde (Fujii and Tonomura, 1972, 1974, 1975; Sahm, 1975; Pilat and Prokop, 1976). Cell extracts of *Pseudomonas oleovorans* (Sokolov and Trotsenko, 1977), *Pseudomonas putida* C1 (Hohnloser et al., 1980), *Hansenula polymorpha* (Van Dijken et al., 1975), *Methylococcus capsulatus* (Patel and Hoare, 1971), *Methanobacterium thermoautotrophicum*, *M. voltae* and *M. jannaschii* (Escalante-Semerena and Wolfe, 1984) and *Alcaligenes faecalis* (Marion and Malaney, 1963) can also oxidize formaldehyde.

Yamamoto et al. (1978) isolated 65 strains of methanol-utilizing bacteria from seawater, sand, mud and weeds of marine origin and found that all were able to use formaldehyde as a sole carbon source for growth. In contrast, Kimura et al. (1977) found that 336 strains of bacteria, isolated from coastal seawater and mud, could not use formaldehyde as a sole carbon source for growth.

2.1.5. Transport.

2.1.5.1. VOLATILIZATION -- The dissolution of gaseous formaldehyde, $(H_2CO)_g$, into water to form hydrated formaldehyde may be described by the following reaction (Chameides and Davis, 1983):

$$(H_2CO)_g \xrightarrow{H_2O} CH_2(OH)_2$$

in which the reciprocal of the Henry's Law Constant (K_s) is described by (Chameides and Davis, 1983):

$$K_s = 7\text{x}10^3 \exp[6425(1/T-1/298)] \text{ M atm}^{-1} \qquad (2\text{-}1)$$

At 25°C (298°K), K_s equals $7x10^3$ M atm^{-1} or $7x10^6$ m/atm-m^3; therefore, Henry's Law Constant is equal to $1.43x10^{-7}$ atm-m^3/m. This value of Henry's Law Constant suggests that formaldehyde is less volatile than water in aqueous solution and that volatilization from the aquatic environment is not expected to be significant (Lyman et al., 1982).

2.1.5.2. **ADSORPTION** -- Information regarding the adsorption of hydrated formaldehyde to particulate organic matter and sediment in water was not located in the available literature as cited in the Appendix. The high water solubility and low K_{ow} of formaldehyde suggest that partitioning from the water column to particulates and sediment is not significant.

2.1.5.3. **BIOACCUMULATION** -- Formaldehyde is a natural metabolic product and is not subject to bioaccumulation and biomagnification (Kitchens et al., 1976).

Experiments performed on a variety of fish and shrimp show no bioconcentration of formaldehyde (Hose and Lightner, 1980; Stills and Allen, 1979).

Estimating the BCF from the equation developed by Veith et al. (1980), Log BCF = 0.76 Log K_{ow} - 0.23, yields a BCF value of 0.2 from the calculated Log K_{ow} value of -0.65 determined by Hansch and Leo (1981).

2.2. AIR

2.2.1. **Chemical Removal Processes.** The chemical removal processes include reaction with hydroxyl radicals, reaction with other radicals generated by photooxidative means, reaction with ozone and photolytic transformations (Cupitt, 1980). The photooxidation and photolysis of formaldehyde under atmospheric conditions have been studied extensively. In air, these removal processes are capable of rapidly transforming formaldehyde to other compounds. Selected data from the literature are discussed below to describe the significance of each mechanism.

2.2.1.1. **PHOTOLYSIS** -- The UV absorption spectrum of gaseous formaldehyde shows significant absorption in the environmentally significant wavelength range between 290 and 370 nm (Kitchens et al., 1976). The absorption of sunlight by formaldehyde present in the atmosphere results in its photodissociation by the following primary process (Horowitz and Calvert, 1978; Calvert et al., 1972; Su et al., 1979; Moortgat et al., 1980; Kitchens et al., 1976):

$$(1)\quad CH_2O + h\nu \rightarrow H + HCO \xrightarrow{O_2} 2HO_2 + CO$$

$$(2)\quad CH_2O + h\nu \rightarrow H_2 + CO$$

The overall rate constant for the photolysis of formaldehyde in air has been reported by various authors; these data along with the corresponding calculated half-lives are summarized in Table 2-1. The photolytic half-life of formaldehyde is <12 hours. As the elevation above sea level increases, the rate of photolytic decomposition increases (Moortgat et al., 1980).

2.2.1.2. **REACTION WITH HYDROXYL RADICALS** -- The reaction of formaldehyde with hydroxyl radicals (•OH) has been described by the following reactions (Niki et al., 1984; Graedel et al., 1976; Leone and Seinfeld, 1984; Bufalini et al., 1977):

$$(1)\quad HO\cdot + CH_2O \rightarrow \cdot CHO + H_2O$$

$$(2)\quad HO\cdot + CH_2O \rightarrow HC(O)OH + H\cdot$$

$$(3)\quad HO\cdot + CH_2O \xrightarrow{O_2} CO + HO_2\cdot + H_2O$$

$$(4)\quad HO\cdot + CH_2O \xrightarrow{O_2} HCO_3 + H_2O$$

TABLE 2-1

Photolysis Rate Constants for Formaldehyde in Air

Rate Constant (K_p) (sec^{-1})	Calculated Half-Life (days)	Reference
$8x10^{-5}$	0.1	Graedel, 1978
$3.2x10^{-5}$ (stimulated sunlight)	0.25	Su et al., 1979
Sea level		
$4.6x10^{-5}$ at 30° zenith angle	0.17	Moortgat et al., 1980
$4.0x10^{-5}$ at 50° zenith angle	0.2	
$2.3x10^{-5}$ at 70° zenith angle	0.35	
10 km high		
$10.3x10^{-5}$ at 30° zenith angle	0.08	Moortgat et al., 1980
$9.4x10^{-5}$ at 50° zenith angle	0.085	
$7.0x10^{-5}$ at 70° zenith angle	0.11	

The rate constant for the reaction between formaldehyde and hydroxyl radicals has been reported by various authors; these data are summarized in Table 2-2. The data from Table 2-2 indicate that the rate constant for this reaction is $\sim 10^{-11}$ cm^3/molecule-sec. Assuming an average atmospheric •OH concentration of 10^6 molecules/cm^3, a half-life of ~0.8 days can be calculated.

2.2.1.3. REACTION WITH OTHER RADICALS -- Formaldehyde reacts with atomic oxygen, O(3P), to form primarily CHO and OH (Chang and Barker, 1979; Klemm, 1979; Klemm et al., 1980). The rate constant for the reaction between formaldehyde and atomic oxygen at ~25°C has been reported to be $\sim 1.5\text{-}1.8 \times 10^{-13}$ cm^3/molecule-sec (Hampson, 1980; Chang and Barker, 1979; Klemm et al., 1980; Herron and Huie, 1973); assuming an average atmospheric atomic oxygen concentration of 2.5×10^4 molecules/cm^3 (Graedel, 1978), a half-life of 5.3 years can be calculated.

Chlorine radicals (Cl•) react with formaldehyde as shown by the following reaction (Niki et al., 1978b):

$$Cl\cdot + CH_2O \rightarrow HCl + \cdot CHO$$

The rate constant (K_{Cl}) at 25°C is 7.8×10^{-11} cm^3/molecule-sec (Niki et al., 1978b); assuming an average atmospheric Cl• concentration of 2×10^4 molecules/cm^3, a half-life of ~5 days can be calculated.

The rate constant for the reaction between singlet oxygen and formaldehyde at room temperature is 23×10^{-19} cm^3/molecule-sec (Penzhorn et al., 1974), indicating no environmental significance.

TABLE 2-2

Rate Constants for the Reaction Between •OH and Formaldehyde

Rate Constant, K_{OH} (cm^3 $molecule^{-1}$ sec^{-1})	Reference
15×10^{-12} at 25°C	Niki et al., 1978a
9.4×10^{-12} at 26°C 6.5×10^{-12}	Atkinson et al., 1979
10.0×10^{-12} at 25°C	Hampson, 1980
14.1×10^{-12}	Edney et al., 1983
14.0×10^{-12} at 25°C	Graedel et al., 1976
9.9×10^{-12} at 25°C	Kerr and Sheppard, 1981
8.4×10^{-12} at 26°C	Niki et al., 1984

Formaldehyde reacts with nitrate radicals in the atmosphere as shown (Atkinson et al., 1984):

$$NO_3 + CH_2O \rightarrow HNO_3 + HCO,$$

with K_{NO3} equal to 3.23×10^{-16} cm^3/molecule-sec, this may be environmentally important as a sink for formaldehyde during the night (NRC, 1982). Formaldehyde can also react with $HO_2\cdot$ radicals, which are generated in the atmosphere (Ve at et al., 1982).

2.2.1.4. REACTION WITH OZONE -- The rate constant for the reaction between formaldehyde and ozone at 27°C has been reported to be 0.2×10^{-23} cm^3/molecule-sec (Hampson, 1980); assuming an average atmospheric ozone concentration of 10^{12} molecules/cm^3, a half-life $>10^4$ years is calculated, indicating no environmental significance.

2.2.2. Physical Removal Processes. The physical atmospheric removal processes include dissolution (wet deposition), adsorption on aerosol particles and dry deposition (Cupitt, 1980). Cupitt (1980) estimated that the physical removal of formaldehyde from the atmosphere is unlikely to be an important chemical removal process.

Gaseous formaldehyde in the atmosphere, however, does undergo dissolution into clouds and rainwater as it has been detected in these media by a number of investigators (Klippel and Warneck, 1978; Zafirou et al., 1980; Saiki et al., 1977; Seki et al., 1977; Munger et al., 1983; Grosjean and Wright, 1983). Kok and Nutall (1980) suggested that rainout may be an important environmental sink for formaldehyde. Once formaldehyde is dissolved into cloud and rainwater, it is susceptible to chemical alteration (Chameides and Davis, 1983; Munger et al., 1983), possibly producing formic acid through the oxidation of hydrated formaldehyde.

In addition to dissolution, formaldehyde can apparently undergo adsorption to aerosol particulates as it has been detected and monitored on atmospheric aerosol (Grosjean, 1982; Klippel and Warneck, 1978, 1980).

2.3. SOIL

2.3.1. Microbial Degradation. Various microbes isolated from soil can biologically degrade formaldehyde. Four formaldehyde-resistant yeasts, Debaryomyces vanrijii and Trichosporon penicillatum strains, completely consumed formaldehyde in a glucose growth medium (Kato et al., 1982). Methylobacterium organophilum strain XX, acclimated to methanol/methane, was also able to degrade formaldehyde (Patel et al., 1978). Numazawa et al. (1974) observed that the soil microbe Micrococcus flavus strain 148 was unable to use formaldehyde as a sole carbon source, but was able to oxidize formaldehyde to formic acid. Kung and Wagner (1970) found that species of Pseudomonas isolated from soil were able to degrade formaldehyde.

As noted in Section 2.1.4., formaldehyde is biodegradable in natural water and in various activated sludges. Therefore, it appears likely that formaldehyde is susceptible to microbial degradation in the natural soil environment.

2.3.2. Chemical Degradation. Pertinent data regarding the chemical degradation of formaldehyde in soil were not located in the available literature as cited in the Appendix.

2.3.3. Leaching/Adsorption. No information concerning the adsorption of formaldehyde to soil were located in the available literature as cited in the Appendix. At high concentrations, formaldehyde gas adsorbs somewhat to clay mineral; this is important for its use as a soil fumigant (De and Chandra, 1978).

The high water solubility and low K_{ow} of formaldehyde suggest that soil adsorption will be low. The K_{oc} of an organic compound may be estimated from its K_{ow} by using the following equation (Kenaga and Goring, 1978): $\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377$. Using the calculated Log K_{ow} of -0.65 (Hansch and Leo, 1981), the K_{oc} value is calculated to be ~5. The K_{oc} estimation from the molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) also yields a K_{oc} value of ~5, which indicates that formaldehyde will have a high mobility in soil.

2.3.4. Volatilization. Experimental data regarding the volatilization of formaldehyde from soil were not located in the available literature as cited in the Appendix. As noted in Section 2.1.5.1., formaldehyde is not expected to volatilize from aquatic environments; however, as water containing formaldehyde evaporates from soil, the formaldehyde can also be expected to evaporate as it is a gas at room temperature.

2.3.5. Persistence. Studies regarding the persistence of formaldehyde in soil were not located and there are no data available to suggest that formaldehyde will persist in the soil environment.

2.4. SUMMARY

Formaldehyde exposed to the aquatic environment exists in the hydrated form, which is not susceptible to hydrolysis or direct photolysis. Microorganisms present in the aquatic environment are apparently capable of degrading formaldehyde in several days under appropriate conditions. Aquatic oxidation by hydroxyl radicals has a calculated half-life of ~400 days. Formaldehyde is not subject to bioaccumulation or biomagnification in aquatic organisms.

Photolysis and reaction with hydroxyl radicals rapidly remove formaldehyde from sunlit atmospheres; the calculated half-life of each process is <1 day. Formaldehyde in the atmosphere can dissolve in cloud and rainwater and be adsorbed onto atmospheric aerosol.

Formaldehyde is susceptible to degradation by soil microorganisms. Estimation methods predict that formaldehyde will be highly mobile in soil and likely to undergo significant leaching.

3. EXPOSURE

3.1. WATER

Formaldehyde can be exposed to the aquatic environment from aqueous discharge effluents generated by formaldehyde production and industrial formaldehyde use (Kitchens et al., 1976). In addition, removal of formaldehyde from the atmosphere by rainfall (dissolution) can also expose surface waters to formaldehyde.

Shackelford and Keith (1976) detected formaldehyde (no concentrations given) in effluents from two chemical plants (one in Louisville, KY) and in the effluent from a sewage treatment plant located on the Upper Catawba River, NC. About 4% of the total effluent from urea and melamine resin production and 0.1% of the phenolic resin effluent generated from the production of these formaldehyde resins was measured as formaldehyde (Kitchens et al., 1976).

Ewing et al. (1977) monitored 14 heavily industrialized river basins in the United States for the presence of pollutants between August, 1975 and September, 1976; formaldehyde was positively identified at a level of 12 ppb in only 1 of 204 sites tested.

Formaldehyde has been detected in rain, fog and cloudwater. Grosjean and Wright (1983) monitored the levels of formaldehyde in the following types of water:

Type	Location	Formaldehyde Concentration (ppm)
ice fog	AK, one site	0.5-1.16
rain	CA, one site	0-0.06
cloud	CA, one site	0.01-1.08
mist	CA, two sites	0.25-0.56
fog	CA, four sites	0.0-2.30

Klippel and Warneck (1978) detected formaldehyde in average concentrations of 0.111-0.174 µg/g H_2O in rainwater in Western Europe. Zafirou et al. (1980) monitored the rainwater at a remote marine atoll located in the central equatorial Pacific; the rainwater averaged ~8 µg formaldehyde/kg. Saiki et al. (1977) and Seki et al. (1977) detected formaldehyde in Japanese rainwater (concentrations not available).

The gross analysis available from the U.S. EPA STORET Data Base contains 1906 observations of formaldehyde in water with maximum and minimum concentrations of 160,000 and 0 ppm, respectively, and a mean concentration of 390.7 ppm.

3.2. FOOD

Formaldehyde may be present in foods either naturally or as a result of contamination (Kitchens et al., 1976). Table 3-1 lists concentrations of formaldehyde occurring naturally in some foods. Formaldehyde has been detected in commercial shrimp at levels of 0.39-2.15 mg/kg (Radford and Dalsis, 1982). Formaldehyde can also be eluted from formaldehyde-resin plastic dishware with water or 4% acetic acid depending upon temperature (Tsuchiya et al., 1975).

Hexamethylenetetramine, which is used as a food additive, may decompose gradually to form formaldehyde under acidic conditions or in the presence of proteins (IARC, 1982).

3.3. INHALATION

3.3.1. Sources of Emissions.

Formaldehyde is emitted to the atmosphere from a variety of man-made sources. The major sources appear to be combustion from stationary sources (e.g., power plants, manufacturing facilities, home fuel consumption, incinerators) and emissions in exhaust from automobiles (gasoline) and diesel-powered vehicles (Kitchens et al., 1976; NRC, 1982).

TABLE 3-1

Concentrations of Formaldehyde Occurring Naturally in Foods*

Food	Concentration (μg/g)
tomato	5.7-7.3
apple	17.3-22.3
cabbage	4.7-5.3
spinach	3.3-7.3
green onion	13.3-26.3
carrot	6.7-10.0
white radish	3.7-4.4

*Source: Tsuchiya et al., 1975

Other sources of formaldehyde emissions include industrial use and manufacturing of formaldehyde, forest fires, tobacco smoke, releases from formaldehyde resin products and animal wastes, petroleum manufacturing, and releases from its use in embalming and fumigation (Graedel, 1978; Kitchens et al., 1976).

3.3.2. Inadvertent Production in the Atmosphere. Formaldehyde is produced in the atmosphere as a result of the photooxidation of various hydrocarbons present in air (Kitchens et al., 1976; Logan et al., 1981; Graedel et al., 1976; Kerr and Shepherd, 1981; Leone and Seinfeld, 1984; Calvert et al., 1972; Lowe and Schmidt, 1983; NRC, 1982). A significant amount of these hydrocarbon precursors to formaldehyde are emitted to the air from automobile exhaust and stationary combustion sources. The exact contribution of formaldehyde exposure to the atmosphere as a result of inadvertent formation from hydrocarbon photooxidation is difficult to quantify; however, Kitchens et al. (1976) suggested that the contribution may be two times greater than the amount released directly from automotive sources.

3.3.3. Monitoring. Formaldehyde has been monitored extensively in the air. Table 3-2 summarizes selected monitoring data available from the literature regarding formaldehyde levels found in the ambient atmosphere. As might be expected from the sites of the major emission sources, the highest levels of formaldehyde have been found in urban and industrialized areas. The lowest levels correspond to clean marine air. In addition, the concentration of formaldehyde in the atmosphere has been observed to decrease with an increase of altitude.

Table 3-3 lists formaldehyde concentrations monitored primarily in indoor sources. The concentrations detected in homes containing formaldehyde-type insulations and resins and levels monitored in funeral homes are

TABLE 3-2

Formaldehyde Monitoring Data for the Ambient Atmosphere

Concentration	Comments	Reference
0.2 ppbv	clean tropical marine air	Lowe and Schmidt, 1983
0.09-0.52 ppbv	nonurban, west coast of Ireland; maximum levels found in clean air in early afternoon	
0.11-0.57 ppbv	remote marine air in central equatorial Pacific	Zafirou et al., 1980
65 ng/m^3	atmospheric aerosol in urban West Germany	Klippel and Warneck, 1978, 1980
≤ 2 ng/m^3	atmospheric aerosol in clear marine air	
5 ng/m^3	atmospheric aerosol in coastal West Ireland	
2-48 ppb	Los Angeles, CA air 1980 (Sept.-Oct.)	Grosjean, 1982
0-264 ng/m^3	Los Angeles, CA particulate phase	
0.1-2.1 ppb	Harwell, England July-August, 1974	Cox et al., 1976
1-47 ppb	unspecified Japanese air	Kenmochi and Ishii, 1979
9-18 $\mu g/m^3$	Ohtsu area, Japan	Suga et al., 1978
0.1-6.5 ppb	typical of central European background	Platt et al., 1979
0.2-0.5 ppb	typical of marine air in Dagebull, Germany	
0.03 ppb	unpolluted marine air in Loop Head, Ireland	Platt and Perner, 1980
0.02-0.5 ppb	moderately. polluted marine air in Dagebull, Germany	
0.0-0.9 ppb	rural German air	
0.1-6.5 ppb	rural polluted air	
0.7-5.1 ppb	urban German air	Neitzert and Seiler, 1981
0.4-3.8 ppb	rural German air	
0.2-1.0 ppb	clean marine air Cape Point, S. Africa	

TABLE 3-2 (cont.)

Concentration	Comments	Reference
1.3 ppb av. <0.1 ppb av.	surface air Julich, W. Germany above 5 km height	Lowe et al., 1980
0.8-2 ppb 0.8-11 ppb 0.8-5 ppb	Pacific Ocean off Japan sea near Borneo and Phillipines Indian Ocean	Fushimi and Miyake, 1980
8.3 ng/m³ mean	Sofia, Bulgaria	Kalpazanov and Kurchatova, 1976
<10 ppb av.	Japanese air; daytime concentration higher than nighttime concentration	Kenmotsu et al., 1982
1-2 ppb av.	Tokyo, Japan; daily maximum usually occurred at noon with yearly maximum during June and August	Matsumura et al., 1979
50-71 ppb	autoexhaust monitoring stations in Tokyo, Japan	Higuchi et al., 1979
7.5 ppb	yearly average at Brookhaven Laboratory, Long Island, NY (July, 1982-May, 1983)	Tanner and Meng, 1984
4 ppb	approximate winter average same site	
15 ppb	approximate summer average same site	
8 ppb	average concentration in Tokyo, Japan (1964-1971)	Yamate and Matsumura, 1972
24-59 ppb	Los Angeles, CA smog (June, 1980)	Hanst et al., 1982
11.2-14.3 ppb	vicinity of automobile-traveled streets in Switzerland	Wanner et al., 1976
3.8-6.6 ppb	daily mean concentration at four New Jersey sites; concentration higher with more traffic and photochemical activity	Cleveland et al., 1977
4-86 ppb	morning air in downtown Los Angeles, CA (September 29-November 13,1981)	Grosjean and Fung, 1984

TABLE 3-2 (cont.)

Concentration	Comments	Reference
11.3 ppb	average concentration St. Louis, MO (May-July, 1980 or March-April, 1981)	Singh et al., 1981, 1982
12.3 ppb	average concentration Denver, CO (May-July, 1980 or March-April, 1981)	
19.0 ppb	average concentration Riverside, CA (May-July, 1980 or March-April, 1981)	
14.3 ppb	average concentration Staten Island, NY (May-July, 1980 or March-April, 1981)	
20.6 ppb	average concentration Pittsburg, PA (May-July, 1980 or March-April, 1981)	
12.0 ppb	average concentration Chicago, IL (May-July, 1980 or March-April, 1981)	
0-1 ppb	clean marine air, West coast of Ireland	Lowe et al., 1981
0.2-2.5 ppb	slightly polluted air Julich, W. Germany	
0-27.0 ppb	749 air samples collected between 1977 and 1980 in suburban/urban U.S. sites; 26% of samples positive with 25% of positives >2.7 ppb	Brodzinsky and Singh, 1982
5.5 ppb	ground level Reims, France	Barbe et al., 1979
0.055 ppb	10 km over Reims, France	
0.0055 ppb	27 km over Reims, France	

TABLE 3-3

Formaldehyde Monitoring Data for Indoor Air

Concentration	Comments	Reference
0.35 ppm median <0.10-3.68 ppm range	survey of 100 Wisconsin homes/trailers containing urea-formaldehyde materials	Dally et al., 1981
33-380 ppb	gas stove in test kitchen; high concentration correlates to nonvented hood; low concentration correlates to hood vent with fan at highspeed	Hollowell et al., 1980
66-216 ppb	indoor concentrations in Med-II residences	
8.3 ppm	maximum concentration observed in offgas from burning of natural gas in household devices	Schmidt and Goetz, 1977
89-708 mg/kg wood	emissions from wood-burning fireplaces	Lipari et al., 1984
0.1-1.2 ppm	concentration exposed to embalmers in funeral homes	Williams et al., 1984
1.33-2.48 ppm	levels above background in academic laboratories using formaldehyde-treated biological specimens	Calusz et al., 1984
0.35-1.39 ppm	average concentrations measured in six different funeral homes	Kerfoot and Mooney, 1975
1 ppm	approximate median concentration measured in an anatomy laboratory	Skisak, 1983
0.06-1.83 ppm	Danish study of 25 new homes using urea-formaldehyde particle board	Anderson et al., 1975
0.58 ppm	average concentration found in 319 Swedish homes	Sundin, 1978
0-3.40 ppm	sampling of homes in Washington State	Breysse, 1977, 1978
<0.41-8.2 ppm	sampling of 68 Connecticut homes insulated with urea-formaldehyde foam	Sardinas et al., 1979

significantly higher than the ambient levels cited in Table 3-2. Pickrell et al. (1983, 1984) measured formaldehyde release rates from various consumer products that are considered to be the source of formaldehyde exposure in air inside homes. Because of its use in embalming, formaldehyde levels are elevated in funeral homes.

3.4. DERMAL

Pertinent data regarding the monitoring of dermal exposure of formaldehyde were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

A number of recent reports assessing the toxicity of formaldehyde have reviewed the pharmacokinetics of the compound in laboratory animals (Squire and Cameron, 1984; CTFA, 1984; Federal Register, 1984).

4.1. ABSORPTION

Formaldehyde, a small water soluble compound, is absorbed by all routes of exposure. Absorption following inhalation was estimated to be 95-100% in anesthetized dogs exposed to 0.15-0.35 μg formaldehyde/ℓ of air and occurred in both upper and lower regions of the respiratory tract (Egle, 1972). Under normal conditions, absorption is expected to occur in the upper respiratory tract (nasal passages in obligate nose-breathers; trachea, bronchi in oral breathers) where first contact occurs (Heck et al., 1983; Gibson, 1982). Absorption continued to be near 100% even when the ventilatory rate of dogs was increased to 20/minute (Egle, 1972). Repeated inhalation exposure to formaldehyde (15 ppm, 6 hours/day for 9 days) in rats did not alter the absorption of the compound by the nasal mucosa (Heck et al., 1983). Assuming 100% absorption in the nasal epithelium, Chang et al. (1983) reported an absorption dose rate of ~0.075 μg/minute/cm^2 nasal mucosa in mice exposed to 6 and 15 ppm formaldehyde (6 hours). In rats exposed to 6 ppm, the absorption rate increased from ~0.060-0.130 μg/minutes/cm^2 during the 6-hour exposure, while rats exposed to 15 ppm absorbed formaldehyde at a rate of ~0.17 μg/minute/cm^2 throughout the 6-hour exposure.

Absorption of formaldehyde from the gastrointestinal tract occurs quite rapidly; radiolabeled compound was detected throughout the body within minutes of oral administration (Loomis, 1979). Blood levels of formaldehyde following oral ingestion are similar to blood levels following inhalation of the compound (Squire and Cameron, 1984). Dermal absorption of formaldehyde occurs to some degree but is not a major route unless exposure is by direct contact with the liquid. Jeffcoat et al. (1983) reported that dermal absorption of formaldehyde (0.1 or 11.2 mg/animal) applied to the backs of rats or guinea pigs was ~55-60%, regardless of dose. Radiolabeled compound collected in air traps (~25% of applied dose) may have been CO_2 metabolites or evaporated parent compound. In cynomolgus monkeys, dermal absorption accounted for <1% of the dermally applied dose (2.0 mg/animal).

4.2. DISTRIBUTION

Autoradiographic studies in mice administered C^{14}-formaldehyde by intravenous injection show a relatively uniform distribution of the radiolabel throughout the body at 30 minutes after treatment (Johansson and Tjalve, 1978). At 24 hours after injection, residual radioactivity levels were low but showed a uniform distribution pattern with little evidence of accumulation. Using a GC/MS technique for identifying unchanged free or reversibly bound (acid labile) formaldehyde, Heck et al. (1982) detected no increased tissue levels in male F-344 rats exposed by inhalation to 6 ppm formaldehyde (6 hours/day) for 10 days when compared with controls. Tissue samples (nasal mucosa, testes, liver and brain) were removed immediately after exposure was terminated. Rapid metabolism (Section 4.3.) or irreversible (covalent) binding of formaldehyde to cellular macromolecules were suggested as causes for the undetectable formaldehyde levels.

4.3. METABOLISM

The metabolism of formaldehyde is somewhat complex because it is a natural body product, formed from the degradation of certain amino acids (histidine, serine, glycine and tryptophan), and is recycled in the single carbon biosynthetic pathways (forming glycine, serine and choline) (Squire and Cameron, 1984). Low levels of formaldehyde normally occur within cells and are often bound reversibly to amino compounds. Exogenous formaldehyde, following systemic exposure, is metabolized by oxidation to formic acid and subsequently to CO_2. The initial oxidation step is apparently very rapid, having a half-life of ~1.5 minutes (determined in monkey blood) (McMartin et al., 1979). The half-life of formic acid before oxidation was somewhat longer (80-90 minutes) but still relatively brief. In mice intravenously injected with formaldehyde, ~29 and 46% of the total CO_2 excreted was eliminated within 15 and 60 minutes of treatment, respectively (Johansson and Tjalve, 1978). Metabolism of formaldehyde by aldehyde oxidase (dehydrogenase) occurs in hepatic mitochondrial preparations (Horton and Packer, 1970; Smith and Packer, 1972; Lewis et al., 1978; Cinti et al., 1976), isolated hepatocytes (Dicker and Cederbaum, 1984) and olfactory and respiratory nasal epithelium (Casanova-Schmitz et al., 1984a). Oxidation of formaldehyde to formic acid has also been demonstrated in erythrocytes, brain, kidney, liver, muscle and adrenals of various species (rat, rabbit, bovine, sheep and humans) (CTFA, 1984).

The metabolism of formaldehyde requires reduced glutathione and NAD (Ku and Billings, 1983, 1984). Apparently, formaldehyde binds to glutathione forming S-hydroxymethylglutathione, which is dehydrogenated to S-formylglutathione. A hydrolase cleaves the glutathione adduct releasing reduced glutathione and formic acid. Cells depleted of glutathione metabolize formaldehyde at a slower rate and show greater cytotoxicity. The suggested mechanism of formaldehyde cytotoxicity was as follows: increased formaldehyde levels deplete glutathione levels thus increasing the presence of free radicals, which then causes lipid peroxidation (Ku and Billings, 1984).

Hemminki (1982) reported the preferential binding of formaldehyde in vitro to cysteine, with less reactivity toward glutathione. The resulting conjugate was thiazolidine-4-carboxylic acid (Hemminki, 1984).

In a review and re-evaluation of the in vivo metabolism of formaldehyde in the rat, Mashford and Jones (1982) administered C^{14}-formaldehyde at 4 and 40 mg/kg by i.p. injection to male Sprague-Dawley rats. As was previously reported by Neely (1964) and Edwards et al. (1970), most of the dose was exhaled as $^{14}CO_2$. At the low dose, 70 and 82% of the administered dose was exhaled as $^{14}CO_2$ at 12 and 48 hours after injection. The higher dose did not appear to alter the metabolic rate or efficiency, with 66 and 78% of the dose eliminated as $^{14}CO_2$ at 12 and 48 hours. Three urinary metabolites were identified in both dose groups within 5 hours of treatment, which accounted for up to 11% of the administered dose. The three urinary metabolites were formic acid (80% of the urinary radioactivity), N,N'-bis(hydroxymethyl) urea (15%) and N-(hydroxymethyl) urea. No free formaldehyde was detected in the urine or expired air. The three studies of the metabolism of formaldehyde in rats are consistent in defining its major metabolic pathways (Figure 4-1). The urinary metabolites, thiazolidine-4-carboxylate, N-hydroxymethylurea, N,N'bis(hydroxymethyl) urea and N,N'-diformylcysteine, are suspected urinary artifacts, produced in the urine following reaction with cysteine or urea (see Figure 4-1) (Mashford and Jones, 1982).

In humans, the excretion of formic acid in the urine has been suggested as a possible monitoring parameter of occupational formaldehyde exposure (Gottschling et al., 1984). The CTFA (1984) suggested that humans may eliminate proportionally more formic acid than rats because of a slower rate of oxidation to CO_2. Due to the normally low levels of formaldehyde

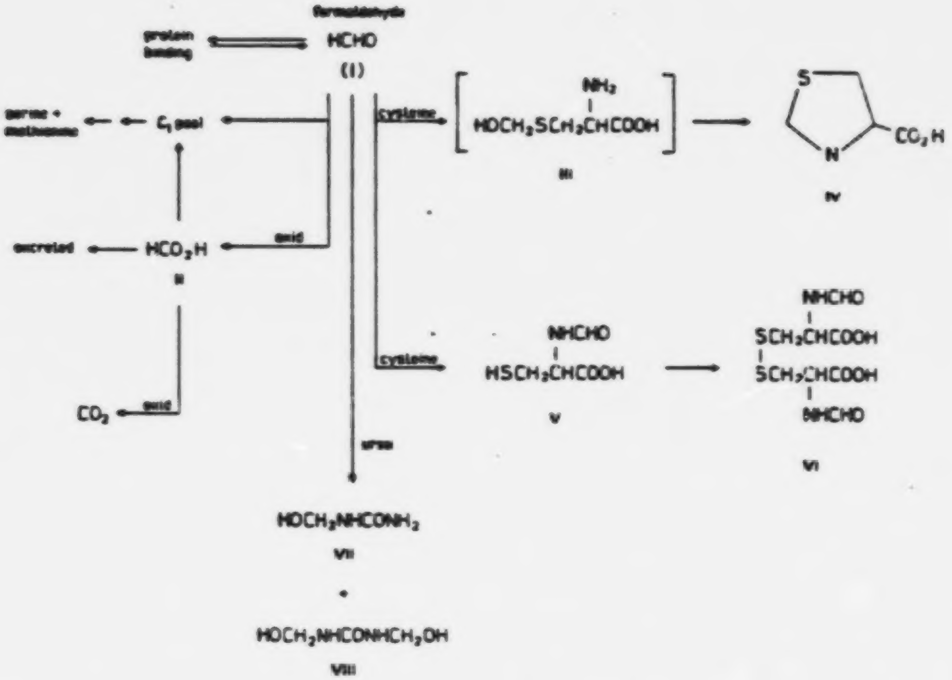

formaldehyde
protein binding
HCHO
(I)
serine + methionine
C1 pool
cysteine
NH2
HOCH2SCH2CHCOOH
III
S
N
CO2H
IV
excreted
HCO2H
II
oxid
NHCHO
SCH2CHCOOH
SCH2CHCOOH
NHCHO
cysteine
NHCHO
HSCH2CHCOOH
V
CO2
oxid
urea
VI
HOCH2NHCONH2
VII
+
HOCH2NHCONHCH2OH
VIII

FIGURE 4-1

The Fate of Formaldehyde in Biological Systems

Incorporation of the carbon atom into the C_1-pool or else oxidation to formate (II) represent true metabolic pathways in the rat. Reaction of formaldehyde with either cysteine or urea produces the urinary artifacts thiazolidine-4-carboxylate(IV),N-hydroxymethylurea(VII) and N,N'-bis-(hydroxymethyl) urea (VIII) within rat urine. Production of N-formylcysteine (V) *in vivo* probably represents a true metabolic pathway in the Wistar rat though oxidation of this in urine produces another artifact, N,N'-diformylcystine (VI).

Source: Mashford and Jones, 1982

exposure (0.5 ppm), highly variable baseline urinary formic acid levels and the small contribution of formic acid from exogenons formaldehyde, this monitoring technique was not deemed feasible (Gottschling et al., 1984).

4.4. EXCRETION

The major route of elimination of metabolites of formaldehyde is the expiration of CO_2. Urinary excretion of formic acid is the secondary route with minor amounts of urinary cysteine and urea conjugates also identified (see Figure 4-1). Free formaldehyde does not appear to be eliminated in the expired air or urine.

The rate of metabolism and elimination of formaldehyde metabolites is rapid. Johansson and Tjalve (1978) reported that ~29 and 46% of the intravenously injected dose (23.6 μmol/kg) was eliminated at 15 and 60 minutes after treatment, respectively. Mashford and Jones (1982) reported that in rats ~70 and 80% of an i.p. dose of formaldehyde was exhaled as CO_2 within 12 and 48 hours, respectively. Buss et al. (1964) reported that ~40% of an oral dose of formaldehyde was eliminated as CO_2 within 12 hours of treatment. Additional data on the excretion kinetics of formaldehyde metabolites were not located in the available literature as cited in the Appendix.

5. EFFECTS

Several review articles (Squire and Cameron, 1984; Van Otten, 1983; Ulsamer et al., 1982; Gibson, 1982; Boreiko et al., 1982a), reports (CTFA, 1984) and agency documents (U.S. EPA, 1983, 1984a; Federal Register, 1984; NRC, 1980; IARC, 1982; NIOSH, 1976, 1981) are available that summarize the toxicological data regarding formaldehyde. In addition, the Chemical Industry Institute of Toxicology (CIIT) has sponsored two conferences on formaldehyde toxicology, from which two books of papers have been compiled (Gibson, 1983a; Clary et al., 1983). Because of the vast amount of information available on the health effects of formaldehyde in animals and humans, it was necessary to concentrate on those studies most relevant to the establishment of chronic toxicity and carcinogenicity risk assessment. This document is a profile of the health effects of formaldehyde and is not intended to be a complete review of the literature.

5.1. CARCINOGENICITY

A review of the carcinogenicity data on formaldehyde in animals and humans has been conducted recently by the U.S. EPA (1984a).

5.1.1. Animal Studies. In an early inhalation study (Horton et al., 1963), groups of 59-60 C3H mice were exposed to formaldehyde vapor at 0.0, 0.05, 0.10 and 0.20 mg/ℓ (0, 50, 100 and 200 mg/m^3) thrice weekly, 1 hour/day for 35 weeks. Mortality and severe toxicity occurred among mice exposed at 0.20 mg/ℓ and treatment was discontinued after 11 exposures. Mortality was 15/60 among the high-dose group but survivors showed histological changes in the trachea and bronchi. Histopathological changes included squamous cell metaplasia (16/35), epithelial stratification (8/35), atypical metaplasia (5/35) and basal-cell hyperplasia (4/35). The same type of histopathological change was diagnosed among mice surviving 35 weeks of treatment (105 exposures) at 0.05 and 0.10 mg formaldehyde/ℓ. The incidence of epithelial stratification, squamous cell metaplasia, basal cell hyperplasia and atypical metaplasia was 14/34, 6/34, 10/34 and 0/34 among mice treated at 0.10 mg/ℓ and 9/23, 0/23, 6/23 and 0/23 among mice exposed to 0.05 mg formaldehyde/ℓ. The incidence of epithelial stratification and squamous cell metaplasia was 4/26 and 3/16 among control group mice. No tumors were observed in those mice inhaling formaldehyde vapors for 35 weeks.

In addition to the 35-week studies, Horton et al. (1963) retained a group of 36 mice surviving exposure at 0.05 mg/ℓ for 35 weeks (3 times weekly, 1 hour/exposure) and subsequently exposed them to 0.15 mg/ℓ formaldehyde vapor for an additional 29 weeks. Metaplastic histopathological changes (incidences not specified) in the respiratory epithelium of these mice had developed deeper within the respiratory tract (to major bronchi), but no tumors were diagnosed.

An inhalation bioassay of formaldehyde in B6C3F1 mice and F344 rats was conducted by Battelle's Columbus Laboratories for CIIT and was reported at an interim period (Swenberg et al., 1980a,b) and as final results (Kerns et al., 1983a,b). Groups of ~120 animals of each sex and species at each dose level were exposed at 0.0, 2.0, 5.6 and 14.3 ppm (0, 2.5, 6.9 and 17.6 mg/m^3) for 6 hours/day, 5 days/week for up to 24 months. Mice surviving the 24-month exposure period were maintained for an additional 3 months of nonexposure before the terminal sacrifice. Rats were observed during a 6-month period of nonexposure after 24 months of exposure. Interim sacrifices of ~10 animals of each sex per exposure level were performed at 6, 12, 18, 24 and 27 months (rats only) before terminal sacrifices at 27 (mice) or 30 months (rats). Gross and histopathological examination of major organs and tissues (~50 tissues/animal) were performed on all available animals.

Mortality of male mice was increased in a dose-related manner with 41, 33, 32, and 25 survivors at 18 months following exposure at 0, 2.0, 5.6 and 14.3 ppm, respectively. Mortality among females was not affected, with 83-92 survivors at 18 months. Histopathological changes in mice were limited to the nasal passages. Squamous cell metaplasia first became apparent in mice exposed at 14.3 ppm for 12 months. By 18 months, dysplasia and metaplasia were more severe in mice exposed at 14.3 ppm; a few mice exposed at 5.6 ppm had nasal epithelial dysplasia (Swenberg et al., 1980a). Proliferative changes in the nasal epithelium became progressively more severe, with ~90% of high-dose mice having dysplasia and metaplasia; a few mice exposed at 5.6 ppm had dysplasia and metaplasia and a few mice exposed at 2.0 ppm had hyperplasia and inflammation at the 24-month sacrifice. Two males exposed at 14.3 ppm developed squamous cell carcinoma of the nasal turbinates by the 24-month sacrifice (Table 5-1). At 27 months, following a 3 month nonexposure period, only mice exposed at 14.3 ppm had dose-related histopathological effects (squamous dysplasia of the nasal epithelium persisted) (Kerns et al., 1983a,b).

In rats, toxic effects were apparent with a dose-related decrease in survival and body weight gain in both sexes. Inhalation of formaldehyde at 14.3 ppm clearly induced the development of carcinoma in the nasal cavity and upper trachea in both sexes of rats. The first grossly visible nasal carcinomas were detected on days 358 and 432 in a female and male rat of the high-dose group. Lesions were first identified microscopically in rats of the high-dose group sacrificed at 6 months. During the later sacrifice intervals, lesions were more prevalent and severe, affecting larger areas of the nasal cavity and occasionally involving nasal bones. When the study was concluded, a total of 51 of 117 males and 52 of 115 females of the high-dose

TABLE 5-1

Incidence of Nasal Cavity Squamous Cell Carcinoma Among Rats and Mice Exposed to Formaldehyde Vapor[a]

Exposure Route	Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Inhalation	mice/ B6C3F1	M	17.6 mg/m^3 6 hours/day, 5 days/week	104 weeks	115 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	2/120 ($p>0.05$)
Inhalation	mice/ B6C3F1	F	17.6 mg/m^3 6 hours/day, 5 days/week	104 weeks	115 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	0/120
Inhalation	mice/ B6C3F1	M/F	6.9 mg/m^3 6 hours/day, 5 days/week	104 weeks	115 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	0/240
Inhalation	mice/ B6C3F1	M/F	2.5 mg/m^3 6 hours/day, 5 days/week	104 weeks	115 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	0/240
Inhalation	mice/ B6C3F1	M/F	0.0 mg/m^3	104 weeks	115 weeks	NA	air only	nasal cavity	squamous cell carcinoma	0/240
Inhalation	rat/F344	M	17.6 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	51/117 ($p<0.001$)
Inhalation	rat/F344	M	17.6 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	52/115 ($p<0.001$)
Inhalation	rat/F344	M	6.9 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	1/119
Inhalation	rat/F344	F	6.9 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	1/116
Inhalation	rat/F344	M	2.5 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	0/118

TABLE 5-1 (cont.)

Exposure Route	Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Inhalation	rat/F344	F	2.5 mg/m^3 6 hours/day, 5 days/week	104 weeks	130 weeks	NS	air/vapor	nasal cavity	squamous cell carcinoma	0/118
Inhalation	rat/F344	F	0.0 mg/m^3	104 weeks	130 weeks	NA	air/vapor	nasal cavity	squamous cell carcinoma	0/118
Inhalation	rat/F344	F	0.0 mg/m^3	104 weeks	130 weeks	NA	air/vapor	nasal cavity	squamous cell carcinoma	0/114

QUALITY OF EVIDENCE

Strengths of Study:	The study included a large number of male and female animals and exposure was of long duration. The formaldehyde concentrations were tested that showed dose-related effects (see Comments). Histopathological analyses were extensive. Statistical analyses were performed.
Weakness of Study:	Data on mice were limited. Only two cases of carcinoma were identified among mice at the highest level tested, therefore limiting classification as carcinogenic in this species.
Overall Adequacy:	Adequate
Comments:	At 6.9 mg/m^3, one squamous cell carcinoma was reported for each group of male (n=119) and female (n=116) rats. The incidence of spontaneous nasal cancers in mice is very low, so that the two cases identified among treated males were regarded as treatment-induced.

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*Source: Kerns et al., 1983a,b

NA = Not applicable; NS = not specified

group had developed nasal cavity squamous cell carcinoma ($p<0.001$) (see Table 5-1). Benign polypoid adenoma occurred among 4/117 males and 1/115 females exposed at 14.3 ppm formaldehyde. The incidence of nasal cavity squamous cell carcinoma among rats exposed at 5.6 ppm was 1/119 for males and 1/116 for females (see Table 5-1). The incidence of nasal carcinoma in this dose group was not significantly increased above controls (0/118 males; 0/114 females) but does show a dose-related trend since nasal cavity carcinomas are very rare in untreated rats (Swenberg et al., 1980b; Kerns et al., 1983a,b). In rats exposed at 5.6 ppm, nonmalignant proliferative lesions included nasal epithelial dysplasia, metaplasia and polypoid adenoma (6 cases among males). The same types of lesions (epithelial dysplasia, squamous metaplasia and 4 males and 4 females with polypoid adenoma) also occurred among rats exposed at 2.0 ppm. These lesions appeared to be primarily reversible effects since they were not apparent in rats killed at 30 months after a 6-month observation period (Kerns et al., 1983a,b). Control rats developed few similar proliferative lesions of the nasal cavity (1/118 polypoid adenoma in males; 0/118 in females).

The carcinogenic effect of formaldehyde and hydrogen chloride vapors, in combination and separately, were examined by Albert (1979) and Albert et al. (1982). Premixing formaldehyde and hydrogen chloride apparently produced bis(chloromethyl)ether; therefore, the carcinogenicity of all three compounds was tested. Five groups of 100 male Sprague-Dawley rats were exposed to formaldehyde alone (14.2 ppm), hydrogen chloride alone (10.2 ppm), premixed formaldehyde and hydrogen chloride (14.3 and 10.0 ppm, respectively), chamber-mixed formaldehyde and hydrogen chloride (14.1 and 9.5 ppm) or air (controls). Animals were exposed for 6 hours/day, 5 days/week for their lifetime. An interim report of this study (Albert et al., 1982) was conducted after 382 exposures (588 days) and indicated a high incidence of nasal squamous cell carcinoma in the formaldehyde-only group and in both formaldehyde-hydrogen chloride groups. The incidence of nasal squamous cell carcinoma was 10/38 in the formaldehyde only group and 18/94 among both formaldehyde-hydrogen chloride groups combined, while none were detected in hydrogen chloride-alone (0/29) or air-exposed control (0/28) groups (Table 5-2). The incidence of nasal cancers among rats exposed only to formaldehyde represents a significant increase ($p=0.001$) compared with air-exposed controls or historical controls. In addition, the incidence of nasal carcinoma was expected to increase since 62 rats of the formaldehyde-only exposure group were still alive at the time of the study.

A group of 88 male Syrian golden hamsters were exposed to 10 ppm formaldehyde vapor for 5 hours/day, 5 days/week for their lifetime (Dalbey, 1982). A group of 132 hamsters were untreated and served as controls. Mortality among exposed hamsters was significantly decreased ($p<0.05$) compared with controls. Gross and histological examinations of all major tissues, with emphasis on the nasal turbinates and respiratory tract, were performed on all available animals. There was no evidence of carcinogenicity among hamsters exposed to formaldehyde. Evidence of toxicity was limited to nasal epithelium hyperplasia and metaplasia in 5% of the exposed hamsters, while no lesions were observed among the control group.

Mueller et al. (1978) examined the carcinogenic effect of formaldehyde on the oral mucosa of rabbits. Using an "oral tank" and muzzle-like apparatus, a solution of 3% formalin (1.1% formaldehyde) was applied to the oral mucosa of six rabbits for 90 minutes/day, 5 times/week for 10 months. In two of the six rabbits, leukoplakia was grossly visible and microscopic examination of the lesions revealed dyskeratosis and intraepithelial carcinoma.

TABLE 5-2

Incidence of Nasal Cancers Among Sprague-Dawley Rats Exposed to Formaldehyde Vapors[a]

Exposure Route	Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Inhalation	rat/ Sprague-Dawley	M	17.5 mg/m^3 6 hours/day, 5 days/week	588 days[b]	588 days[b]	purified	air/vapor	nasal cavity	squamous cell carcinoma	10/38 (p=0.001)[b]
Inhalation	rat/ Sprague-Dawley	M	0.0 mg/m^3	588 days	588 days[b]	purified	air/vapor	nasal cavity	squamous cell carcinoma	0/28

QUALITY OF EVIDENCE

Strengths of Study:	The number of animals per group was large. The duration at this interim period was long but was being continued for the animals' lifespan. Appropriate controls and statistical comparisons were made.
Weakness of Study:	Only male rats were exposed. Formaldehyde was administered at only one dose level.
Overall Adequacy:	Adequate
Comments:	These data are preliminary, but spontaneous nasal tumors are rare in rats and the incidence reported among formaldehyde-exposed animals is expected to be dose-related. A final report of this study will be necessary to confirm these preliminary results.

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[a] Source: Albert et al., 1982

[b] Data reported are preliminary, since the study was still in progress and was intended to continue for the lifespan of the animals. Tumor incidence may be expected to be higher since 62 and 72 of the treated and control rats, respectively, were surviving.

Subcutaneous injection of 1 mℓ of 0.4% formaldehyde once weekly for 15 months produced local and remote sarcoma development in rats (Watanabe et al., 1954). Among a group of 10 rats treated in this manner, 2 developed subcutaneous injection site sarcomas, 1 a liver sarcoma and 1 a peritoneal sarcoma. A control group was not included for comparison.

In skin irritation-promotion studies in CD-1 mice (Krivanek et al., 1983) and Sencar mice (Spangler and Ward, 1983), formaldehyde did not appear to be a complete carcinogen or tumor initiator. In CD-1 mice formaldehyde also had no promoting activity, while very slight promoting activity was shown in Sencar-strain mice. In a bladder-injection study (Akaza et al., 1984) formaldehyde caused papillary carcinoma of the urothelium in 2 of 3 rats (Sprague-Dawley) treated for 18-22 days and sacrificed at 60 days. The formaldehyde (0.37%) was infused continuously by a mini-pump and catheter into the bladder. In a group of six rats sacrificed at 28 days, after 18-22 days of formaldehyde infusion, two papillomas and one hyperplasia were reported (Akaza et al., 1984).

5.1.2. **Human Studies.** Several reviews of the health and carcinogenic effects of formaldehyde on exposed humans have been conducted (Griesemer et al., 1982; Squire and Cameron, 1984; Wendlick, 1983; Siegel et al., 1983; Clark, 1983). These reviews and a recent literature search identified at least five studies of workers exposed to formaldehyde during its production or use and six studies specifically regarding morticians, medical personnel or pathologists exposed to formalin.

Harrington and Shannon (1975) studied a group of 2079 pathologists and 12,944 technicans exposed to formaldehyde between 1955 and 1973. Based on mortality records, cause of death was determined for 151 pathologists and 154 technicans who were compared by age and year of death with mortality statistics for England, Scotland or Wales. The number of deaths from cancer of the respiratory and digestive tract was lower in pathologists and technicians compared with expected rates. Death from lymphoma was cited for 8 male pathologists while only 3.3 were expected, but this cancer occurred in three technicians and 3.8 were expected. This study does not demonstrate an increased risk of cancer based on the limited number of deaths among pathologists and technicans. There was, however, an increase in the number of suicidal deaths among pathologists and technicans with 27 observed vs. 11 expected. In an update of this study of British pathologist, Harrington and Oakes (1984) reported that the excess of lymphoma deaths was no longer present but deaths from brain tumors were in excess (6 cases observed vs. 2 expected, $p<0.02$). Deaths from nasal or respiratory tract tumors were less than expected. Suicidal deaths continued to be significantly increased (9 observed vs. 2.2 expected).

Doll and Peto (1976, 1977) identified a group of 853 doctors (from a group of 34,440) who were expected to have chronic exposure to formaldehyde in scientific research, pathology or biochemistry. Death from cancer was reported in 39 of the 220 deaths among the cohort. Oral, esophageal or lung cancer accounted for 11 deaths, which was 69% of the expected number. The 28 deaths from other types of cancer represented 90% of the expected number of cancer deaths among 220 total deaths.

Walrath and Fraumeni (1983a,b) conducted a mortality analysis of 1106 deceased morticians who were exposed to formaldehyde for chronic periods through their use of embalming fluids. Mortality rates for the United States were used to determine age, sex and time-specific PMRs for deaths from specific cancers and from cancer in general. The observed number of deaths from malignant neoplasms was 210 vs. 1937 expected, having a PMR of

108. Eight cases of skin cancer (4 malignant melanoma) were observed while 32 were expected, which represents a significant ($p<0.01$) increase (PMR=253) (Table 5-3). Skin cancer deaths appeared to correlate well with the extent of formaldehyde exposure since PMR values were highest when determined for morticians practicing for at least 35 years (PMR=354) and for morticians practicing embalming but not funeral directing (PMR=337). Based on the 6 cases of kidney cancer and 6 cases of brain and CNS cancer among morticians licensed only in embalming, SMR values of 256 and 245 were determined, suggesting a possible association with formaldehyde exposure. Deaths from respiratory tract cancers were almost equal to expected cases (63 observed vs. 61.9 expected; SMR=102).

Levine (1982) and Levine et al. (1983a) presented data from a mortality study of 1477 Canadian undertakers exposed during 1928-1957. Based on deaths as of December 31, 1977, there was no significant increase in mortality from cancer in general, with fewer deaths from lung, skin and prostate cancer and slightly more cases of brain cancer than expected. Jensen and Andersen (1982) attempted to correlate 84 cases of lung cancer among physicians (case-control study) to formaldehyde exposure by their medical specialty. No cases of lung cancer occurred among doctors specializing in pathology and few occurred among doctors who had ever been employed in pathology, forensic medicine or anatomy. Matanoski (1980) studied the incidence of cancer deaths among 510 pathologists and reported a slight (not significant) excess of biliary, hepatic, pancreas lung, kidney, brain and lymphoid cancer. The two observed cases of hypopharyngeal cancer were reported to be 30.6 times the expected number.

Several studies have been conducted on workers exposed to formaldehyde during its production or use in the textile industry. In addition to

TABLE 5-3

Incidence of Skin Cancer Among Humans Exposed to Formaldehyde[a]

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
Dermal, inhalation and oral	1106	U.S. mortality rates	M,F[b]	NR	NS	skin	cancer	8[c]	3.16	SMR = 253

QUALITY OF EVIDENCE

Weakness of Study: The level of exposure to formaldehyde was not reported and the duration of exposure was not specified. The number of deaths from cancer was small and limited the ability to detect increased mortality among the exposed workers.

Overall Adequacy: Inadequate

Comments: The SMR was higher in workers licensed for >30 years and those licensed for embalming only and not for embalming and funeral directing.

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[a] Source: Walrath and Fraumeni, 1983a,b

[b] 1101 males and 5 females

[c] Four cases were melanomas.

NR = Not reported; NS = not specified

epidemiological studies, Halperin et al. (1983) reported a case of squamous cell carcinoma in a 57-year-old man who was exposed to formaldehyde for 25 years in a fabric-finishing industry. Wong (1983) conducted a mortality study on a group of 1975 chemical plant workers employed from 1940-1977. Death certificates for 136 of 146 deceased workers were used to determine cause of death. Comparisons of observed deaths were made with age- and time-specific United States mortality rates. The total number of cancer deaths (n=37) was equal to the expected number (SMR=101). The number of cancer deaths for specific sites was not significantly increased for any cancer type, but small numbers of deaths limited statistical analyses. Cancers of the prostate (4 observed vs. 1.3 expected) brain (3 vs. 1.61) and Hodgkins disease (2 vs. 0.83) were slightly increased, while respiratory tract cancers (12 vs. 12.36) were almost equal to expected numbers and digestive tract cancers (5 vs. 9.46) were less prevalent than expected.

A group of 2490 male chemical plant workers who were employed for at least 1 year in the production and use of formaldehyde was used in a mortality study by Marsh (1982). Workers were employed between 1949-1966 and the study period was 1950-1976. A total of 592 deaths was confirmed; based on work histories, 136 occurred among employees having at least 1 month of exposure to formaldehyde. Among the formaldehyde-exposed decedents, 22 cancer deaths had occurred. A matched cohort group of 456 nonexposed decedents from the same plant and United States mortality rates were used for comparison. The total number of cancer deaths among the formaldehyde-exposed workers was less than expected (SMR=86). Deaths from cancer of the digestive tract and peritoneum (9 cases:SMR 126.8) were in excess of the expected number, while other site-specific cancers were fewer than expected.

Among workers exposed for ≤ 5 years and allowed a latency period of ≥ 20 years, there was a significant increase ($p<0.01$) in digestive tract cancer (5 cases observed vs. 1.56 expected; SMR=320) (Table 5-4). Marsh (1982) noted that exposures were to many chemicals (vinyl chloride, polystyrene, amino plastics, polyvinyl butyral, cellulose acetate and phenol) and mortality patterns may have been influenced by these chemicals, or combinations, in addition to formaldehyde.

A case-control study of cancer deaths among formaldehyde-exposed DuPont workers was conducted by Fayerweather et al. (1983). A total of 142 cancer deaths was identified among workers with potential exposure to formaldehyde. Exposure to formaldehyde was determined by job classification and categorized by level of exposure and whether exposure was continuous or intermittent. Smoking histories of workers were also considered. Among workers exposed to formaldehyde for ≥ 5 years, 8 prostate and 4 bladder cancer deaths occurred while 2 and 1, respectively, occurred among the control group. These cancer sites were considered "unlikely sites for the action of formaldehyde" and the few cases did not allow a definite conclusion. There was no apparent association between deaths from cancer of various sites of the respiratory tract and exposure to formaldehyde. Exposure level and duration (years of employment at a job involving formaldehyde exposure) also had no apparent effect on cancer distribution. Smoking habits clearly had an effect on the occurrence of lung and respiratory cancers among workers.

A proportionate mortality study by Liebling et al. (1984) identified a group of 24 decedents of a chemical plant who had been exposed to formaldehyde. Based on the limited number of deaths, these data are speculative. A total of 10 cancer deaths occurred, slightly more than expected (PMR=156).

TABLE 5-4

Incidence of Digestive Cancer Among Humans Exposed to Formaldehyde*

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
Dermal, inhalation and oral	136	U.S. mortality rates	M	NR	≥1 month, ≤5 years	digestive system	cancer	5	1.56	320 ($p<0.01$)

QUALITY OF EVIDENCE

Weaknesses of Study: The levels of formaldehyde encountered were not measured or estimated. The number of cancer deaths were too few for valid conclusions.

Overall Adequacy: Inadequate

Comments: The incidence of digestive cancers was increased only in the group of workers exposed for <5 years and having at least 20 years of latency.

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*Source: Marsh, 1982

NR = Not reported

Four cases of colon and rectal cancer (PMR=424) and two cases of buccal and pharyngeal cancer (PMR=952) were significantly increased ($p \leq 0.05$) but the limited number of cases diminish the prominence of these apparent excesses. Duration of exposure to formaldehyde was not determined, exposure levels of formaldehyde ranged from 0.05-5.00 ppm (1 sample was 273 ppm, however) and were usually ~1 ppm. Liebling et al. (1984) also noted that most of the workers were exposed to other chemicals including cellulose acetate, polyvinyl butyral, polystyrene, vinyl chloride and amino plastics.

Acheson et al. (1984) conducted a mortality study of 7680 men working in one of six factories where formaldehyde was produced or used. Workers were classified into one of four formaldehyde exposure levels by job title as follows: background <0.1 ppm, low 0.1-0.5 ppm, moderate 0.6-2.0 ppm, high >2.0 ppm (based on recollection of irritant effects). A total of 1619 deaths were observed (1862 expected) and 455 were due to malignancies (468 expected). An analysis of respiratory tract cancer deaths revealed no observed nasal cancers (1.07 expected), 205 lung cancer deaths (215 expected), 5 buccal and pharyngeal cancer deaths (4.6 expected), 4 laryngeal cancer deaths (4.5 expected) and no nasopharyngeal cancer deaths. Mortality from lung cancer did not correlate with level of formaldehyde exposure or length of service in jobs involving exposure to formaldehyde (Table 5-5). In response to the finding of other epidemiology studies (reviewed previously), Acheson et al. (1984) reported that leukemias (9 observed vs. 114 expected) and brain cancer deaths (5 observed vs. 12.5 expected) were less prevalent among the formaldehyde-exposed workers than expected.

In a case-control study of 598 deaths from carcinomas of the bronchus, 296 occurred among men who were occupationally exposed to formaldehyde (Coggon et al., 1982). This number represented a 1.5-fold increase (relative risk=1.5; p<0.001) over the number of matched controls with formalde-

TABLE 5-5

Incidence of Lung Cancer Among Chemical Plant Workers Exposed to Formaldehyde*

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure (ppm)	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
Occupational (inhalation)	7680	National Registry Data	M	<0.1	NS	lung	cancer	37	43	SMR = 86
				0.1-0.5	NS	lung	cancer	39	42	SMR = 92
				0.6-2.0	NS	lung	cancer	14	21	SMR = 67
				>2.0	NS	lung	cancer	109	97	SMR = 112

QUALITY OF EVIDENCE

Strengths of Study: A large cohort of formaldehyde-exposed workers was studied. Exposure was estimated and respiratory tract cancer incidence was analyzed based on exposure level and length of service.

Weaknesses of Study: Workers were exposed to many chemicals during their employment in the chemical factories.

Overall Adequacy: Limited

Comments: No association between respiratory cancer and formaldehyde exposure in humans is shown.

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*Source: Acheson et al., 1984

NS = Not specified

hyde exposure. A dose-related response was not suggested, however, since 44 cases of bronchial carcinoma occurred among workers having high exposure to formaldehyde and a similar proportion of controls (nonbronchial carcinoma deaths) had high exposure to formaldehyde (relative risk=0.9). The evidence was regarded as presumptive in showing an association between formaldehyde exposure and bronchial carcinoma. Coggon et al. (1982) suggested that the increased incidence associated with formaldehyde may also be associated with polycyclic aromatic hydrocarbon exposure or tobacco consumption.

Siegel et al. (1983) reviewed a study of textile workers (Moss and Lee, 1974) and one of leather workers (Decoufle, 1979), which suggested an association between occupational formaldehyde exposure and the development of cancer. Moss and Lee (1974) reported 1482 deaths among male textile workers with 31 deaths from tongue, mouth or pharyngeal cancer. This number represented a 77% increase above expected cases, which was a significant ($p<0.01$) excess. Exposure to cotton and wool fibers and dust were regarded as having a greater association with the increased cancers than exposure to formaldehyde. Among leather workers (Decoufle, 1979), an excess of cancers of the upper respiratory tract, urinary bladder and lymphoma were reported. Workers were exposed to many chemicals in addition to formaldehyde; therefore, attributing the increase to any one chemical is impossible.

5.2. MUTAGENICITY

The mutagenicity data for formaldehyde have been summarized in a number of reviews (Auerbach et al., 1977; CTFA, 1984; Squire and Cameron, 1984; Griesemer et al., 1982; NRC, 1980). Both positive and negative results have been reported in the Ames Salmonella reverse-mutation assay. Positive mutagenic activity has been shown in assays with other bacteria species (Escherichia coli; Pseudomonas fluorescen; Staphylococcus aureus), yeast and fungi (Saccharomyces cerevisiae; Neurospora crassa; Aspergillus nidulans) and *Drosophila*. In mammalian cell systems *in vitro*, formaldehyde has been shown to have mutagenic activity in the L5178Y mouse lymphoma assay but not in CHO cells or C3H/10T1/2 mouse embryo cells. Sister chromatid exchanges in CHO cells and human lymphocytes were induced by formaldehyde treatment (CTFA, 1984). Because of the numerous reviews and the abundance of mutagenicity data on formaldehyde, this review will concentrate on relatively recent data.

A review of the recent mutagenicity assays for formaldehyde is presented in Table 5-6. In general, formaldehyde appears to have weak mutagenic activity. In microbial assays in *Salmonella typhimurium* and fungi (*S. cerevisiae*, *N. crassa*), both forward and reverse mutations have been shown. Using repair-deficient strains of *E. coli*, formaldehyde has been shown to cause DNA damage, primarily single-stranded breaks. In *Drosophila melanogaster*, forward gene mutations and sex-linked recessive lethal mutations have been produced when formaldehyde was ingested in the diet (Benyajati et al., 1983; Szabad et al., 1983).

Various *in vitro* mammalian assays have been employed to test the mutagenicity of formaldehyde (see Table 5-6). Some indicators of mutagenic activity of formaldehyde in cultured-cell systems include an increased frequency of transformed mouse embryo cells (Rundell et al., 1983), chromatid aberrations in hamster lung fibroblasts (Ishidate et al., 1981), and chromosomal aberrations and SCEs in CHO cells (Natarajan et al., 1983). Martin et al. (1978) reported increased unscheduled DNA synthesis in HeLa cells exposed to formaldehyde (10^{-6} to 10^{-8} M). In cultured human cells, forward mutations (Goldmacher et al., 1983; Goldmacher and Thilly, 1983), chromosome aberrations (Levy et al., 1983), DNA-protein crosslinks and single stranded breaks in DNA (Grafstrom et al., 1983) and SCEs (Kreiger and Garry, 1983) have been induced by formaldehyde treatment.

TABLE 5-6

Summary of Mutagenicity Data for Formaldehyde

Assay	Indicator/ Organism	Compound Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Bacterial reverse mutation	*Salmonella typhimurium*	NS	plate incorporation	up to 3600 µg/plate or toxic dose	+/- S9	-	Strains TA100, TA1535, TA1538, TA1537, TA98	Gocke et al., 1981
	S. typhimurium	NS	liquid suspension	2-10 µg/mℓ	NS	+	Slightly positive in TA100	Couch et al., 1982
	S. typhimurium	NS	plate assay	2-10µg/mℓ	NS	-	No increase in revertants in TA100 or TM677	Couch et al., 1982
	S. typhimurium	NS	plate assay	100 µg	NS	+	Slightly positive in TA102, TA2638	Levin et al., 1982
	S. typhimurium	as formalin (40% aq. sol. with MeOH)	plate assay	up to 200 µg/plate	+/-	+	Positive in TA100, slightly positive in TA98; negative in strains UTH8414 and UTH8413	Connor et al., 1983
	S. typhimurium	NS	plate assay	0.5-2.0 mM	+/-	+	Increased revertants in TA100, TA98, TA97	Donovan et al., 1983
	S. typhimurium	as formalin (37%)	plate assay	up to 10 mg/plate or toxic dose	+/-	+	Tested in strains TA1535, TA100, TA1537, TA98; usually positive in TA100	Haworth et al., 1983
	S. typhimurium	NS	plate assay	up to toxicity limit	+/-	-	Tested in strains TA1535, TA100, TA1538, TA98, TA1537	DeFlora et al., 1984
Bacterial forward mutation	*S. typhimurium*	NS	liquid suspension	2-8 µg/mℓ	NS	+	Weakly mutagenic at 8-azaguanine gene in TM677	Couch et al., 1982
	S. typhimurium	as formalin (37% aq. sol.)	liquid suspension	0.17-2.0 mM	+/-	+	Mutagenicity was decreased with metabolic activation; mutation to 8-azaguanine resistance in TM677	Temcharoen and Thilly, 1983

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Bacterial forward mutation	S. typhimurium	as formalin (37% aq. sol.)	liquid suspension	0.17-2.0 mM	+/-	+	8-azaguanine resistance in TM677	Goldmacher and Thilly, 1983; Goldmacher et al., 1983
Bacterial forward mutation	S. typhimurium	NS	liquid suspension	0.06-0.25 mM	NS	+	8-azaguanine resistance in TM677	Donovan et al., 1983
DNA-repair assay	Escherichia coli	NS	liquid suspension	up to 8 µg/well	+/-	+	Toxic to repair deficient strains WP67 and CM871; metabolic activation did not increase effect	DeFlora et al., 1984
	E. coli	NS	spot test	10 µl/disc	-	+	Increased inhibition in repair deficient strains	DeFlora et al., 1984
	E. coli	NS	spot test	NS	-	+	Slight preferential inhibition of DNA pol A^- strain	Rosenkranz, 1972
Forward mutation	Saccharomyces cerevisiae	NS	plate test	0.05-0.4 mM	-	+	Weak mutation in strains N123, XV185-14C, OH2252-6a and XV423-3A	Chanet and Von Borstel, 1979
	Neurospora crassa	NS	NS	NS	-	+	Potent mutagen in strain H-50 (uvs-2) and weak mutagen in H-12 (uvs-2^+)	Brockman et al., 1981; DeSerres, 1983
Forward gene mutation	Drosophila melanogaster	formaldehyde	diet	0.1% in diet	NA	+	Four alcohol dehydrogenase gene mutant strains produced	Benyajati et al., 1983
	D. melanogaster	formalin (36% aq. sol.)	diet	5×10^{-3} M	NA	+	Eye and wing color mutations (mosaic patterns)	Szabad et al., 1983
Sex-linked resessive lethal	D. melanogaster	formalin (36% aq. sol.)	diet	5×10^{-3} M	NA	+	4.7% lethal mutants produced	Szabad et al., 1983

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Cell transformation	mouse embryo fibroblasts (C3H/10T1/2C18)	as formalin (37%)	*In vitro*; fluid medium	0.1-2.5 µg/mℓ	-	-	Treatment did not increase cell transformation	Ragan and Boreiko, 1981; Boreiko et al., 1982b; Frazelle et al., 1983
Chromosomal aberrations	Chinese hamster lung fibroblast	NS	*In vitro*; liquid medium	0.018 mg/mℓ	+/- S9	+	Chromatid aberrations were produced	Ishidate et al., 1981
Cell mutation	CHO cells	NS	*In vitro*; collagen gel	up to 50 µg/ℓ vapor	-	-	Formaldehyde was cytotoxic over the dose range tested	Zamora et al., 1983
SCE	CHO cells	from paraformaldehyde	*In vitro*; liquid medium	0.003-0.024 µℓ/mℓ	+/-	+	Increased frequency of chromosomal aberrations and sister chromatid exchanges; metabolic activation reduced mutagenic activity	Natarajan et al., 1983
Cell transformation	mouse embryo cells (BALB/C-3T3)	NS	*In vitro*; liquid medium	0.5-2.5 µℓ/mℓ	-	+	Increased frequency of transformed cells ($p<0.01$)	Rundell et al., 1983
Unscheduled DNA synthesis	HeLa cells	NS	*In vitro*; liquid culture medium	$10^{-\text{[illegible]}}$ to $10^{-\text{[illegible]}}$ M	-	+	Slight increase in the induction of unscheduled DNA synthesis	Martin et al., 1978
	rat tracheal cells	NS	*In vitro* on collagen substrate	100 µM	-	-	No increase in DNA-repair	Doolittle and Butterworth, 1984
Forward mutation	human cells TK6 lymphoblastoid line	analytical grade formalin (37% aq. sol.)	*In vitro*, liquid medium	up to 150 µM	-	+	Trifluorothymidine resistance increased in dose-related manner	Goldmacher et al., 1983; Goldmacher and Thilly, 1983
DNA damage	human bronchial cells	NS	*In vitro*	up to 1.0 mM	-	+	DNA-protein crosslinks and single strand DNA breaks	Grafstrom et al., 1983

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Chromosome aberrations	human fibroblasts	NS	In vitro; liquid medium	2, 4, 8 mM x 15 minutes	-	+	0.66, 1.53, 4.71% chromosome aberrations compared with 0.31% in controls	Levy et al., 1983
SCE	human lymphocytes	commercial formalin and paraformaldehyde	In vitro; fluid medium	0.1-50 μg/mℓ	-	+	SCE counts were significantly ($p<0.05$) increased after exposure to commercial and pure samples at 5-50 μg/mℓ	Kreiger and Garry, 1983
Micronucleus test	NMRI mice	NS	In vitro, i.p.	10, 20, 30 mg/kg, i.p. 1 dose	NA	-	No significant increase in micronucleated polychromatic erythrocytes	Gocke et al., 1981
	CBA mice	from paraformaldehyde	In vito, i.p.	6.25, 12.50, 25.00 mg/kg, i.p.	NA	-	No increase in micronuclei compared to controls	Natarajan et al., 1983
SCE	rats	NS	In vivo; inhalation	0.5, 6, 15 ppm 6 hours/day, 5 days	NA	-	No increase in SCE or chromosomal aberrations of lymphocytes	Kligerman et al., 1984
DNA damage	rats	NS	In vivo; inhalation	0.47, 2.0, 5.9 or 14.8 ppm for 1, 3 or 5 days	NA	-	No increase in DNA repair in tracheal epithelial cells	Doolittle and Butterworth, 1984
Dominant lethal test	Q-strain male mice	35% formaldehyde	In vivo, i.p.	50 mg/kg	NA	+/-	Preimplantation losses were increased in rats bred to males at 1 and 3 weeks after treatment	Fontignie-Houbrechts, 1981
Recessive spot test	C57BL/63XT mice	NS	In vivo, inhalation	6.0, 18.0 mg/m^3 6 hours/day, days 8, 9, 10 of pregnancy	NA	-	No increase in the incidence of progeny with fur cobration spots	Jensen and Cohr, 1983
Human chromosome aberrations	humans	occupational exposure	In vivo; inhalation (occupational)	<5 ppm x 28 years of exposure	NA	-	No significant increase in lymphocyte chromosome aberrations compared with controls	Fleig et al., 1982

NA = Not applicable; NS = not stated

The mutagenicity of formaldehyde in various mammalian assay systems has not been established (see Table 5-6). The lack of demonstrable evidence of mutagenesis by formaldehyde following _in vivo_ exposure may reflect its rapid metabolism and detoxication (see Section 4.3.). Doolittle and Butterworth (1984) found no evidence of increased SCEs or chromosomal aberrations in rat tracheal epithelial cells following inhalation exposure (for 1-5 days) at levels near that causing nasal tumors in rats (see Section 5.1.).

The possible mechanism of the mutagenic action of formaldehyde has been suggested by numerous investigators (Poverennyi et al., 1975; Magana-Schwencke and Ekert, 1978; Kubinski et al., 1981; Fornace, 1982; Casanova-Schmitz and Heck, 1983; Casanova-Schmitz et al., 1984b) to be the formation of methylene bridges between DNA strands and other macromolecules. The result is the formation of nucleic acid or nucleic acid-protein adducts. Single-stranded DNA breaks occur as a result of these cross-links. Casanova-Schmitz et al. (1984b) reported evidence of covalent binding of formaldehyde to respiratory mucosal DNA and RNA following a single inhalation exposure (6 hours) at 2-15 ppm. Maximal binding occurred at 6 ppm formaldehyde exposure and was decreased at higher concentrations. Covalent binding to proteins also occurred, increasing linearly with increasing exposure level.

5.3. TERATOGENICITY

Reviews of the available data on the teratogenicity of formaldehyde have been conducted by the NRC (1980), Barlow and Sullivan (1982), Staples (1983) and CFTA (1984).

The teratogenicity of formaldehyde was examined in CD-1 mice following gastric intubation of a 1% (v/w) aqueous solution (12-15% methanol was included in the stock formaldehyde solution) on days 6-15 of gestation

(Marks et al., 1980). Groups of 29-35 female mice were given doses at 74, 148 or 185 mg/kg/day and a group of 76 control mice were given distilled water by gavage. Mortality was high in the group treated at 185 mg/kg/day with 22 deaths among 34 mice by day 18 of gestation. Marks et al. (1980) suggested that methanol, which represented ~60-75 mg/kg/day at the high-dose level of formaldehyde, may have contributed to the lethality. Dams were killed on day 18 of gestation and their uteri were examined. There was a dose-related increase in the average percent of fetal deaths and resorptions/litter and a decrease in the average number of live fetuses in the high-dose group, but these changes were not statistically different from controls. The average weight gain during pregnancy of dams treated at 74 mg/kg/day was decreased ($p<0.01$) compared with controls, but no similar effect was evident in dams given higher formaldehyde doses. The incidence of malformed fetuses was not significantly increased among formaldehyde-treated litters (4/311, 2/336 and 1/83 total fetuses from dams treated at 74, 148 and 185 mg/kg/day, respectively) compared with controls (3/832 fetuses). The few malformations reported were of various types, indicating that formaldehyde did not cause a limited number of one type of malformation. Formaldehyde, therefore, was apparently not embryotoxic or teratogenic at doses that were toxic and lethal to dams.

In a study by Merkurjewa et al. (1983), formaldehyde was administered to pregnant rats in the drinking water to provide doses of 0.02 and 5.0 mg/kg (total or daily dose not specified). The duration and gestational interval of exposure was not available. Formaldehyde treatment resulted in an increase in fetal resorptions and preimplantation deaths. Liver glucose-6-phosphatase and N-acetyl-β-D-glucosaminidase were decreased in the dams and fetuses. No malformations among fetuses were reported.

Hurni and Ohder (1973) studied the effects of dietary formaldehyde on the reproductive capacity and fetal development of Beagle dogs. Pregnant bitches were fed a diet containing 0, 125 or 375 ppm formaldehyde, which provided doses of 0, 3.1 and 9.4 mg/kg/day, on days 4-56 of gestation. Pregnancy rate, litter size and stillbirth frequency were not affected. No malformations were reported among stillborn fetuses or progeny sacrificed at 9 months of age. Body weight of the pups was decreased in a dose-related manner by 5 and 13% of control weights from birth through 8 weeks of age. Behavior and development of maintained progeny were normal, with no effects on reproduction in a limited number retained in the breeding colony.

Overman (1981) tested the effect of dermally applied formaldehyde on the embryo development of hamsters. Formaldehyde, as formalin (dose not specified), was applied to the shaved backs of pregnant hamsters for 2 hours daily on days 7-11 of gestation. Dams were killed on day 15 of gestation and uteri and fetuses were examined. Effects specifically occurring in formaldehyde-exposed fetuses were not reported, but minimal toxic effects and few malformations occurred among groups treated with various compounds.

In a series of Russian studies (Gofmekler, 1968; Gofmekler et al., 1968; Pushkina et al., 1968; Gofmekler and Boneshevskaya, 1969), formaldehyde was administered by inhalation to rats at 0.01 ppm (0.012 mg/m^3) and 0.8 ppm (1.0 mg/m^3) continuously from 10 days before mating and throughout pregnancy. Methodological details of the study were limited. There was no evidence of an increased incidence of malformations among formaldehyde-treated neonates. The average number of fetuses per dam was reported to be reduced in a dose-related manner, but available data did not support this statement. Fetal body weights were increased in both dose groups compared with controls and increased adrenal, thymus and kidney weights were reported. Histological and biochemical (ascorbic acid and nucleic acid levels) changes of the liver and kidneys of fetuses were reported.

In another Russian study (Sheveleva, 1971), rats were exposed by inhalation to formaldehyde at 4 or 0.4 ppm (5.0 or 0.50 mg/m^3) for 4 hours/day on days 1-19 of gestation. Groups of 21 rats were exposed, with 15 killed on day 20 of gestation and 6 per group allowed to deliver. Uteri and fetuses were examined for external malformations. There was no apparent effect on the number of corpora lutea/dam, live fetuses/dam, embryonic or fetal deaths or fetal weight, and no malformations were observed. Slight signs of maternal toxicity were reported among dams exposed at 4 ppm formaldehyde. No clear dose-related effects having biological significance were reported among neonates exposed _in utero_ to formaldehyde (Sheveleva, 1971; Barlow and Sullivan, 1982).

In a Russian study (Shumilina, 1975) of humans exposed to formaldehyde from urea-formaldehyde resins, there was an increased frequency of anemia among women exposed during pregnancy and suggestive evidence of decreased birth weight of babies of exposed mothers.

5.4. OTHER REPRODUCTIVE EFFECTS

Data regarding the effects of formaldehyde on reproductive capacities were reviewed by Barlow and Sullivan (1982), who indicated that exposures to high levels of formaldehyde, even for brief periods, may cause a "stressor" situation that results in hormonal changes and may alter gonadotropic hormone levels. Pseudopregnancy and dioestrus have been induced in female rats by acute formaldehyde treatments (subcutaneous and inhalation) (Chatterjee, 1965; Hagino, 1968). In a fertility study using male rats (Guseva, 1972) and a dominant lethal study using male mice (Epstein et al., 1972), no effect on reproductive capacity occurred among formaldehyde-treated animals. Cassidy et al. (1983) reported that formaldehyde (100 or

200 mg/kg single oral dose) had no effect on testicular weight in rats examined 11 days after treatment. At the high-dose level, however, an increase in the number of sperm per gram of testis and percent of sperm head abnormalities were significantly increased ($p<0.001$). The biological significance of these spermatogenic changes was not discussed and effects on reproductive capacity were not demonstrated.

In women exposed to formaldehyde vapors through occupational exposure to urea-formaldehyde resins (Shumilina, 1975), menstrual disorders were reported among 47.5% with dysmenorrhea being the most common disorder. Menstrual disorders occurred among 18.6% of matched controls. Dysmenorrhea was often reported by older women (age 30-40 years), and decreased estrogen levels were also reported among women with menstrual disorders. In a study of hospital equipment sterilizing personnel, there appeared to be no association between formaldehyde exposure, either before or during pregnancy, and increased spontaneous abortions (Hemminki et al., 1982).

5.5. CHRONIC TOXICITY

The chronic toxicity of formaldehyde has been reviewed by the NRC (1980), the U.S. EPA (1983), CTFA (1984), Solomons and Cochrane (1984) and Squire and Cameron (1984).

Data regarding the chronic toxicity of formaldehyde ingested by the oral route are limited. In a study designed to examine the chronic toxic effects of formaldehyde ingested in formaldehyde-stabilized meat, Casley-Smith (1977) fed 50 rats meat pretreated with formaldehyde on 5 days/week for 12 months (dose level of available formaldehyde not reported). Based on gross observations during the study and histopathological examinations of major organs including the stomach and ileum, the authors concluded that formaldehyde caused no toxic effects. In a teratogenicity study by Marks et al. (1980) (see Section 5.3.), formaldehyde was administered by gavage to mice at 74, 148 or 185 mg/kg/day on days 6-15 of gestation. Mortality was 22/34 and 1/35 among dams treated at 185 and 148 mg/kg/day, respectively. No mortality occurred at the low dose and no increase in malformations was reported among any treated group.

The toxic effects of long-term inhalation of formaldehyde were studied in C3H mice exposed at 0, 0.05, 0.10 and 0.20 mg/ℓ (0, 50, 100 and 200 mg/m³), for 1 hour/day, 3 days/week for 35 weeks (Horton et al., 1963). Mortality in the group exposed at 0.2 mg/ℓ reached 25% (15/60 dead) within the first 3 weeks of exposure; therefore, this study group was discontinued after 11 exposures. Weight gain of mice treated at the lower two dose levels was normal and gross appearance indicated that these dose levels were well tolerated. Histopathological examination of the trachea, bronchi and lungs was performed. Tracheal lesions in the 0.10 mg/ℓ group included basal cell hyperplasia (10/34), epithelial stratification (14/34) and squamous cell metaplasia (6/34). In the 0.05 mg/ℓ group, tracheal lesions included 9 of 23 stratified epithelia and 6 of 25 basal-cell hyperplasia. Among the control group (26 lung pairs examined), three squamous cell metaplasias and four stratified epithelial lesions were reported.

Horton et al. (1963) also exposed a group of 36 mice to formaldehyde vapor at 0.05 mg/ℓ (1 hour/day, 3 days/week) for 35 weeks, and additionally at 0.15 mg/ℓ for the rest of their lifetime. Mortality among this group was high with all mice dying between weeks 35 and 68 of exposure. A group of 30 unexposed controls all survived until the terminal sacrifice at 71 weeks. Metaplastic epithelial changes of the respiratory tract were similar to those seen in mice treated at lower doses for 35 weeks. Lesions were more extensive, however, affecting the major bronchi. No tracheal, bronchial or pulmonary tumors developed among these mice (15 survived for ≥59 weeks).

Groups of 25 male albino rats were exposed to formaldehyde vapor by inhalation at 0, 0.012, 0.035, 1.0 or 3.0 mg/m³ continuously for 3 months (Fel'dman and Bonashevskaya, 1971). Signs of toxicity were limited to rats exposed at 1.0 or 3.0 mg/m³ with no adverse effects at lower dose levels. Toxic effects among rats exposed at the two highest exposure groups included proliferation of lymphohistiocytic elements in the interalveolar walls, and peribronchial and perivascular spaces with moderate hyperemia. Hepatotoxicity, evident in rats exposed at 1.0 and 3.0 mg/m³, was manifested as nuclear polymorphism, numerous binuclear cells surrounding the triads, focal hyperplasia, enlargement and thinning of RNA granules and decreased glycogen content. In addition, the renal cortex of rats in the two highest dose groups showed vasodilation in the juxtamedullary zone, and the parietal region of the cerebral cortex showed focal glial proliferation. These data are supported by the findings of Misiakiewicz et al. (1977), in which rats treated with 1.0 mg formaldehyde vapor/m³ for long-term (unspecified) continuous exposure developed morphological changes in the upper respiratory tract (unspecified) and had decreased liver weight.

The chronic inhalation study by the CIIT (Kerns et al., 1983a,b) using mice and rats exposed to formaldehyde vapor for 24 months can be used for determining chronic toxic effects. Groups of 119-121 animals of each sex of F344 rats and B6C3F1 mice were exposed at 2.0, 5.6 or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week. Interim sacrifices were made at 6, 12, 18 and 24 months and surviving mice were maintained for 3 additional months of non-exposure. Complete histological examination of ~40 tissues/animal, including five sections within the nasal cavity, were performed on all available animals that died or were killed during the study. An exposure-related decrease in body weight was seen in rats exposed at 5.6 and 14.3 ppm over the 24 months of exposure. Histological changes in the nasal epithelium progressed in an exposure-related (dose level and duration) manner. At 24 months, squamous metaplasia was present in almost 100% of the rats exposed at 2.0 ppm, invading the anterior-most regions of the nasal turbinates. In the group exposed at 5.6 ppm, squamous metaplasia was present in almost 100% of the rats but invaded anterior and mid-portions of the nasal turbinates. All areas of the nasal cavity were affected by squamous metaplasia in rats exposed at 14.3 ppm formaldehyde and a high incidence of squamous cell carcinoma (103/232) occurred among this group (see Section 5.1.). In mice, inhalation of formaldehyde was also associated with nasal squamous hyperplasia. These lesions were most frequent and severe in mice exposed at 14.3 ppm, with less extensive lesions in mice of the 5.6 ppm group. Mice exposed at 2.0 ppm formaldehyde had no nasal hyperplasia but a few animals had serous rhinitis. Two male mice exposed at 14.3 ppm developed squamous cell carcinomas in the nasal cavity (see Section 5.1.). Chronic toxic effects of formaldehyde on tissues/organs other than the nasal epithelium were not reported and either did not occur or were not discussed, since nasal effects were emphasized (Kerns et al., 1983a,b).

Dalbey (1982) exposed a group of 88 male Syrian golden hamsters to formaldehyde vapor at 10 ppm (12.3 mg/m^3) for 5 hours/day on 5 days/week for their lifetime. Survival time of the treated hamsters was significantly ($p<0.05$) reduced compared with a group of 132 untreated controls. Histopathological examinations were only performed on the nasal and respiratory tracts. Both hyperplasia and metaplasia of the nasal epithelium were observed in 5% of the treated hamsters, while no similar lesions occurred in control animals.

Coon et al. (1970) exposed rats, guinea pigs, rabbits, squirrel monkeys and dogs continuously to formaldehyde vapor at 4.6 mg/m³ for 90 days. The group consisted of 15 Sprague-Dawley or Long-Evans derived rats (both males and females), 15 Princeton guinea pigs (both sexes), 3 male New Zealand rabbits, 3 male squirrel monkeys and 2 male beagle dogs. Except for one death among the treated rats, no gross signs of toxicity were apparent. Histopathological examination revealed interstitial inflammation in the lungs of all species. Rats and guinea pigs also showed focal inflammatory changes in the heart and kidneys. Coon et al. (1970) were uncertain if the histological changes were attributable to inhalation of formaldehyde. Histological appearance in comparison with the control group was not discussed.

A 26-week inhalation study of the toxic effects of formaldehyde vapor on rats, hamsters and monkeys was conducted by Rusch et al. (1983a,b). Groups of 20 male and 20 female Fischer rats, 10 male and 10 female Syrian golden hamsters and 6 male cynomolgus monkeys were exposed at 0.19, 0.98 and 2.95 ppm (0.23, 1.2 and 3.6 mg/m³) for 22 hours/day, 7 days/week for 26 weeks. Two air-exposed control groups, consisting of the same number of animals as in each treatment group, were maintained for comparison. There was no mortality among any species or dose group as a result of formaldehyde inhalation. There were no signs of toxicity, gross or histological, among any species exposed at 0.19 or 0.98 ppm formaldehyde. In the 2.95 ppm exposure group, rats developed squamous metaplasia (23/37) and basal cell hyperplasia (25/37) in the nasal turbinates, had decreased body weights (apparent after 2 weeks of exposure) and decreased liver weights. In monkeys exposed at 2.95 ppm, hoarseness, congestion and squamous cell metaplasia in the nasal turbinates (6/6) developed. The incidence of squamous metaplasia and basal cell hyperplasia in controls rats was 5/77 and 4/77, respectively. No monkeys from the control groups developed squamous metaplasia (0/12). Hamsters exposed at all test concentrations showed no signs of toxicity to formaldehyde inhalation.

A subchronic inhalation toxicity study of formaldehyde aerosol has been conducted using rabbits exposed for 3 hours/day for up to 50 days (Ionescu et al., 1978). Exposures were to a 3% formaldehyde aerosol in closed chambers. The number of exposed rabbits was not reported. Interim kills were conducted after 3, 7, 15, 21, 30 and 40 days with the final sacrifice at 50 days. Enzyme changes and cytological histology of the bronchopulmonary tract were determined. Enzyme changes included a progressive increase of acid phosphatase, Tween-60-esterase, and naphthol-AS-D-acetate-esterase activities and a rapid decrease in leucyl-aminopeptidase and β-glucuronidase. Cytohistological changes included a progression from epithelial hyperplasia and hypertrophy to metaplasia, dysplasia, destructive and fibrotic lesions and bronchiolectasia. Epithelial involvement was also progressive, with major bronchi affected early and lesions occurring deeper within the pulmonary bronchioles after prolonged exposure.

Chronic exposure to formaldehyde in humans has been associated with respiratory symptoms and mucosal irritation (Griesemer et al., 1982; Barnes, 1983). Alexandersson et al. (1982) reported eye and throat irritation as well as evidence of bronchoconstriction (reduced expiratory flow) among 47 carpentry shop workers exposed to formaldehyde (0.47 mg/m^3), dust (0.5 mg/m^3) and some terpenes (average <4 mg/m^3). Among histology technicans exposed to formaldehyde and xylene, mucous membrane and respiratory irritation and altered respiratory function were reported (Kilburn et al., 1983).

Respiratory effects associated with 3 ppm formaldehyde exposure among three groups of workers (total of 390 workers) included reduced forced-exhalation volume and decreased pulmonary function (Johnson et al., 1983). Based on questionnaires and pulmonary function tests of 105 morticians (intermittent exposure at 0.2-2.1 ppm formaldehyde), Levine et al. (1984) reported no lasting effects on pulmonary function or chronic bronchitis associated with formaldehyde exposure. Main and Hermann (1984) conducted a questionnaire and pulmonary function study of 38 iron foundry workers exposed to formaldehyde (0.18-3.9 ppm) and dust (silica was 0.001-0.155 mg/m^3). Eye and throat irritation occurred during the work period and decreased forced expiration volume occurred but was not persistent. Battista et al. (1979) found an increase in acute bronchitis, pneumoconiosis and cytological changes among cast iron foundry workers. Effects were associated with exposure to silicate, carbon monoxide, sulfur dioxide, phenol, ammonia and formaldehyde. Goldmann et al. (1983) found no chronic effects on pulmonary function or increase in nasal or pulmonary disease among a group of 199 workers exposed during the manufacturing and handling of formaldehyde. Several studies have reported mucous membrane irritation, headache and tiredness among persons exposed to formaldehyde vapors from urea-formaldehyde foam, particle board or plywood construction materials (Garry et al., 1980; Godish, 1981; Harris et al.,, 1981; Cockcroft et al., 1982; Olsen and Dossing, 1982; Konopinski, 1983; Main and Hogan, 1983; Anderson et al., 1983). Formaldehyde levels in newly constructed homes ranged from <0.1 ppm to ~3.0 ppm (Anderson et al., 1983). Based on the toxic effects of formaldehyde following subchronic and chronic exposure indoors, the use of urea-formaldehyde foam insulation in residential and school buildings has been banned by the Consumer Product Safety Commission (Federal Register, 1982).

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of formaldehyde has been reviewed by CTFA (1984), Van Otten (1983) and IARC (1982). A summary of representative median lethal levels (LD_{50} or LC_{50}) of formaldehyde for several animal species is given in Table 5-7. In general, oral LD_{50} values range from 500-800 mg/kg and the inhalation LC_{50} is near 450-500 ppm for rats (Van Otten, 1983). Toxic effects following acute sublethal inhalation of formaldehyde include upper respiratory tract cytotoxicity, with possible proliferation (Kamei et al., 1981; Morgan et al., 1983; Chang et al, 1983; Swenberg et al., 1983; Buckley et al., 1984) and depressed respiratory rate (Chang et al., 1981; Jaeger and Gearhart, 1982; Chang et al., 1983; Buckley et al., 1984; Steinhagen and Barrow, 1984). These studies show that mice exposed to formaldehyde have substantially reduced tidal volume and respiratory rates (as well as general depression of body metabolism), thereby reducing the net formaldehyde dose. Rats, however, show only a reduced tidal volume but no change in respiratory rate. These differences in response to formaldehyde vapor result in different absorbed doses and have been implicated as the cause for carcinogenic effects in rats but not mice exposed at the same dose levels (see Section 5.1.). Acute effects of formaldehyde after intravenous injection in rats included sympathomimetric depression (similar to depressed respiration following inhalation), increased blood pressure and decreased heart rate (Egle and Hudgins, 1974). Inhalation of formaldehyde at 15 ppm (6 hours/day for 21 days) had no effect on immune function and host resistance to infection in B6C3F1 mice (Dean et al., 1984). Based on the sensitization of humans to formaldehyde (CTFA, 1984), Lee et al. (1984) exposed guinea pigs to formaldehyde by inhalation and dermal and subcutaneous (footpad) injection, and tested for pulmonary hypersensitivity, dermal

TABLE 5-7

LD_{50} Values for Formaldehyde in Various Species

Species	Route	LD_{50} or LC_{50}	Reference
Rat	oral	800 mg/kg bw	Smyth et al., 1941
	inhalation	479 ppm (4 hours)	Van Otten, 1983
	subcutaneous	420 mg/kg bw	Skog, 1950
	intravenous	87 mg/kg bw	Langecker, 1954
Mouse	inhalation	399 ppm	Van Otten, 1983
	subcutaneous	300 mg/kg bw	Skog, 1950
Rabbit	dermal	270 mg/kg bw	Lewis and Tatken, 1980
Guinea pig	oral	260 mg/kg bw	Smyth et al., 1941

sensitivity and serum antibodies. Skin sensitivity occurred in hamsters treated by all routes but no pulmonary hypersensitivity or antibodies to formaldehyde were observed.

Acute effects of formaldehyde in humans are similar to those in animals (NRC, 1980; Van Otten, 1983). Lethal doses of formaldehyde (37% formaldehyde) ingested orally have ranged from 30-120 mℓ, with 90 mℓ (523 mg/kg) considered a lethal dose (within 48 hours). Exposure to formaldehyde vapor causes upper respiratory tract, eye and skin irritation. Allergic dermatitis and sensitization from exposure to formaldehyde have been observed in humans (CTFA, 1984). Two cases of asthma have been associated with exposure to formaldehyde; recurrent exposure provoked the condition (Hendrick et al., 1982).

Several laboratory exposure studies in humans have been conducted that provide dose response data regarding the irritant effects of formaldehyde vapor. These studies are summarized in Table 5-8. In addition to the irritant effects, Anderson (1979) and Anderson et al. (1983) reported a decreased nasal-mucus flow rate, but no changes in pulmonary function have been reported. Effects from these brief, low-level exposures are not long-lasting. The average detectable odor level of formaldehyde was ~0.1 ppm (Anderson et al., 1983).

TABLE 5-8

Summary of Clinical Studies with Formaldehyde[a]

Concentration (ppm)	Duration of Exposure	Number of Subjects	Percent of Subjects Responding	Effects	Reference
0.03-3.2[b]	35 minutes	33	45	No significant change in eye blinking rate	Weber-Tschopp et al., 1977
			36	Doubling of eye blinking rate	
			19	Increases in eye blinking rate	
0.03-2.1[b]	20 minutes	33	33	Doubling of eye blinking rate	Weber-Tschopp et al., 1977
			20	"Desire to leave the room"	
			10	Medium eye irritation	
			7	Strong odor, strong eye irritation	
1.6	5 hours/day x 4 days	16	94	"Slight discomfort," conjunctival irritation, dryness of nose and throat	Anderson, 1979
0.83	5 hours/day x 4 days	16	94	"Slight discomfort," conjunctival irritation, dryness of nose and throat	Anderson, 1979
0.03-0.5[b]	5 minutes	33	11	Doubling of eye blinking rate	Weber-Tschopp et al., 1977
			3	"Desire to leave room"	
			2	Medium eye irritation	
0.42	5 hours/day x 4 days	16	31	"Slight discomfort," conjunctival irritation, dryness of nose and throat	Anderson, 1979

TABLE 5-8 (cont.)

Concentration (ppm)	Duration of Exposure	Number of Subjects	Percent of Subjects Responding	Effects	Reference
0.25	5 hours/day x 4 days	16	19	"Slight discomfort," conjunctival irritation, dryness of nose and throat	Anderson, 1979
2.0	40 minutes	10	NS	"Bad odor," eye and throat irritation and headache, no no bronchoconstriction	Schachter et al., 1984
2.0	40 minutes[c]	10	NS	"Bad odor," eye and throat irritation and headache, no no bronchoconstriction	Schachter et al., 1984

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[a] Source: NRC, 1980

[b] Total exposure for 35 minutes at concentrations increasing from 0.03 to 3.2 ppm.

[c] 10 minutes of moderate exercise

NS = Not specified

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Acute toxicity tests of formaldehyde to various species of freshwater fish are abundant (Table 6-1). Many studies have been conducted to determine toxic and safe levels of formaldehyde because the compound, as formalin, is used for therapeutic control of fungal infections and ectoparasites in fish culture. As a result, many data are reported as concentrations of formalin (37% formaldehyde), which have been converted to concentrations of formaldehyde.

Southgate (1950) exposed rainbow trout, *Salmo gairdneri*, to formaldehyde at 10 mg/ℓ for 3 days with no apparent toxic effects. Exposure at 50 mg/ℓ was lethal to trout within 1-3 days. In tests conducted by the State of Washington (Anonymous, 1960), the "critical level" for severe toxic effects during 72-hour exposures was <31.8 mg formaldehyde/ℓ for rainbow trout and <28.2 mg/ℓ in chinook salmon, *Oncorhynchus tshawytscha*. Schneider (1979) reported that the 48-hour LC_{50} in rainbow trout was 160.0 mg formalin (37% formaldehyde)/ℓ or ~59.2 mg formaldehyde/ℓ. Willford (1966) conducted toxicity tests of formaldehyde (administered as formalin) in four species of trout, bluegill sunfish and channel catfish. From the mortality data of 10 concentration tests, the 24- and 48-hour LC_{50} values for rainbow trout, *S. gairdneri*, brown trout, *Salmo trutta*, brook trout, *Salvelinus fontinalis*, and lake trout, *Salvelinus namaycush*, were 76.6 and 62.2, 120.3 and 68.5, 72.5 and 58.1, and 81.4 and 61.8 mg formaldehyde/ℓ, respectively. Lysak and Marcinek (1972) determined permissible (no mortality), toxic (<100% mortality) and lethal (LC_{100}) levels of formaldehyde in rainbow trout. The established levels, following 48-hour exposures, were 20-32, 40-60 and 64 mg/ℓ, respectively. A battery of toxicity tests have

TABLE 6-1

Acute Lethal Effects of Formaldehyde to Freshwater Fish

Species	Duration (hours)	Concentration (mg/ℓ)	Method	Effect	Reference
Rainbow trout *Salmo gairdneri*	72	10	static	no effect	Southgate, 1950
	72	50	static	lethality	Southgate, 1950
	72	31.8	static	lethality	Anonymous, 1960
	48	59.2	static	LC_{50}	Schneider, 1979
	24	76.6	static	LC_{50}	Willford, 1966
	48	62.2	static	LC_{50}	Willford, 1966
	48	20-32	static	permissible level	Lysak and Marcinek, 1972
	48	40-60	static	toxic effects	Lysak and Marcinek, 1972
	48	64	static	lethal effects	Lysak and Marcinek, 1972
	1	200	static	hepatotoxic effects	Williams and Wootten, 1981
	3	492	NS	LC_{50}	Bills et al., 1977
	6	262	NS	LC_{50}	Bills et al., 1977
	24	120	NS	LC_{50}	Bills et al., 1977
	96	47.2	NS	LC_{50}	Bills et al., 1977
Brown trout *Salmo trutta*	24	120.3	static	LC_{50}	Willford, 1966
	48	68.5	static	LC_{50}	Willford, 1966
Brook trout *Salvelinus fontinalis*	24	72.5	static	LC_{50}	Willford, 1966
	48	58.1	static	LC_{50}	Willford, 1966
Lake trout *Salvelinus namaycush*	24	81.4	static	LC_{50}	Willford, 1966
	48	61.8	static	LC_{50}	Willford, 1966
	6	241	NS	LC_{50}	Bills et al., 1977
	24	56.4	NS	LC_{50}	Bills et al., 1977
	96	40.0	NS	LC_{50}	Bills et al., 1977
Chinook salmon *Oncorhynchus tshawytscha*	72	28.2	static	lethality	Anonymous, 1960
Atlantic salmon *Salmo salar*	3	564	NS	LC_{50}	Bills et al., 1977
	6	336	NS	LC_{50}	Bills et al., 1977
	24	156	NS	LC_{50}	Bills et al., 1977
	96	69.2	NS	LC_{50}	Bills et al., 1977
Bluegill sunfish *Lepomis macrochirus*	24	68.5	static	LC_{50}	Willford, 1966
	48	51.8	static	LC_{50}	Willford, 1966
	72	30.4	static	LC_{50}	Helms, 1967
	3	916	NS	LC_{50}	Bills et al., 1977
	6	640	NS	LC_{50}	Bills et al., 1977
	24	84.4	NS	LC_{50}	Bills et al., 1977

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/ℓ)	Method	Effect	Reference
Bluegill sunfish *L. macrochirus*	96	40.0	NS	LC_{50}	Bills et al., 1977
	24	53.7	static	LC_{50}	Schneider, 1979
	48	34.0	static	LC_{50}	Schneider, 1979
	96	25.2	static	LC_{50}	Schneider, 1979
Green sunfish *Lepomis cyanellus*	24	129	NS	LC_{50}	Bills et al., 1977
	96	69.2	NS	LC_{50}	Bills et al., 1977
	72	>34.2	static	LC_{50}	Helms, 1967
Largemouth bass *Micropterus salmoides*	24	45.7	static	0% mortality	Carmichael, 1983
	24	68.5	static	90% mortality	Carmichael, 1983
	24	102.6	static	100% mortality	Carmichael, 1983
	72	>38	static	LC_{50}	Helms, 1967
	72	28.5	static	LC_0	Helms, 1967
	6	412	NS	LC_{50}	Bills et al., 1977
	24	113	NS	LC_{50}	Bills et al., 1977
	96	57.2	NS	LC_{50}	Bills et al., 1977
Smallmouth bass *Micropterus dolomieui*	24	88.8	NS	LC_{50}	Bills et al., 1977
	96	54.4	NS	LC_{50}	Bills et al., 1977
Striped bass *Roccus saxatilis*	24	31.0	static	LC_{50}	Wellborn, 1969
	48	11.8	static	LC_{50}	Wellborn, 1969
	96	6.7	static	LC_{50}	Wellborn, 1969
Channel catfish *Ictalurus punctatus*	24	50.7	static	LC_{50}	Willford, 1966
	48	35.5	static	LC_{50}	Willford, 1966
	96	18.5	NS	LC_0	Clemens and Sneed, 1958, 1959
	96	25.5	NS	LC_{50}	Clemens and Sneed, 1958, 1959
	96	46.6	NS	LC_{100}	Clemens and Sneed, 1958, 1959
	3	190	NS	LC_{50}	Bills et al., 1977
	6	92.8	NS	LC_{50}	Bills et al., 1977
	24	48.8	NS	LC_{50}	Bills et al., 1977
	96	26.3	NS	LC_{50}	Bills et al., 1977
Black bullhead *Ictalurus melas*	72	17.1	static	LC_{50}	Helms, 1967
	24	69.2	NS	LC_{50}	Bills et al., 1977
	96	24.8	NS	LC_{50}	Bills et al., 1977
Golden shiner *Notemigonus crysoleucus*	72	23.6	static	LC_{50}	Helms, 1967

TABLE 6-1 (cont.)

Species		Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
American eel Anguilla rostrata	glass stage	96	31.1	static	LC_{50}	Hinton and Eversole, 1978, 1979, 1980
	black stage	96	83.1	static	LC_{50}	Hinton and Eversole, 1978, 1979, 1980
	yellow stage	96	122.1	static	LC_{50}	Hinton and Eversole, 1978, 1979, 1980
Carp Cyprinus carpio		72	>26.6	static	LC_{50}	Helms, 1967
		2	74	NS	LC_{50}	Suzuki and Kimura, 1977
Zebrafish Brachydanio rerio		96	31	static	LC_0	Wellens, 1982
		96	41	static	LC_{50}	Wellens, 1982
		96	50	static	LC_{100}	Wellens, 1982
Golden orfe Leuciscus idus		48	10	static	LC_0	Wellens, 1982
		48	22	static	LC_{50}	Wellens, 1982
		48	25	static	LC_{100}	Wellens, 1982
		48	12.9	NS	LC_0	Juhnke and Luedemann, 1978
		48	9.6	NS	LC_0	Juhnke and Luedemann, 1978
		48	32.4	NS	LC_{50}	Juhnke and Luedemann, 1978
		48	15.0	NS	LC_{50}	Juhnke and Luedemann, 1978
		48	39.0	NS	LC_{100}	Juhnke and Luedemann, 1978
		48	22.8	NS	LC_{100}	Juhnke and Luedemann, 1978
Harlequin fish Rasbora heteromorpha		24	76	static	LC_{50}	Alabaster, 1969
		48	50	static	LC_{50}	Alabaster, 1969
Tilapia Tilapia sp.		72	>38.0	static	LC_{50}	Helms, 1967

NS = Not stated

been conducted by Bills et al. (1977) to determine maximum safe-use levels of formalin for a number of sport fish species. Median lethal concentrations of formaldehyde (tested as formalin) were 492, 262, 120 and 47.2 mg/ℓ in rainbow trout exposed for 3, 6, 24 and 96 hours, respectively. In the lake trout, Salvelinus namaycush, 6-, 24- and 96-hour LC_{50} values were 241, 56.4 and 40.0 mg formaldehyde/ℓ. Bills et al. (1977) reported 3-, 6-, 24- and 48-hour LC_{50} values at 564, 336, 156 and 69.2 mg/ℓ, respectively. Factors causing increased toxicity of formaldehyde to rainbow trout were high water temperature, soft water and high pH levels (Bills et al, 1977).

Bluegills, Lepomis macrochirus, and channel catfish, Ictalurus punctatus, appeared to be equally or slightly more sensitive to formaldehyde than the trout species, having 24- and 48-hour LC_{50} values of 68.5 and 51.8 mg/ℓ and 50.7 and 35.5 mg/ℓ, respectively, (see Table 6-1) (Willford, 1966). Schneider (1979) reported 24-, 48- and 96-hour LC_{50} values of 53.7, 34.0 and 25.2 mg formaldehyde/ℓ for bluegills. Bills et al. (1977) reported that the 3-, 6-, 24- and 48-hour LC_{50} values were 916, 640, 84.4 and 40.0 mg formaldehyde/ℓ in bluegills. The green sunfish was slightly more resistant, having 24- and 96-hour LC_{50}s at 129 and 69.2 mg/ℓ, respectively. Clemens and Sneed (1958) reported LC_0, LC_{50} and LC_{100} values for formaldehyde in fingerling channel catfish following exposures of 1-96 hours. These values were 32.2 mg formaldehyde/ℓ at 24 hours and 25.5 mg formaldehyde/ℓ at 48, 72 and 96 hours. For exposure times of 24-96 hours, the LC_0 and LC_{100} values were 18.5 and 46.6 mg formaldehyde/ℓ, respectively.

Largemouth bass, Micropterus salmoides, were exposed to formalin at 9.2-153.9 mg formaldehyde/ℓ for 24 hours (Carmichael, 1983). No deaths occurred at ≤45.7 mg/ℓ, while 90% mortality was reported in fish exposed at 68.5 mg/ℓ and 100% mortality occurred following exposures at ≥102.6 mg/ℓ. Helms (1967) reported that the 72-hour LC_{50} for largemouth bass was >38 mg formaldehyde/ℓ and the maximum nonlethal dose was 28.5 mg/ℓ. Bills et al. (1977) reported 6-, 24- and 96-hour LC_{50} values at 412, 113 and 57.2 mg formaldehyde/ℓ in the largemouth bass. The smallmouth bass, *Micropterus dolomieui*, was similarly sensitive with 24- and 96-hour LC_{50} values at 88.8 and 54.4 mg/ℓ, respectively. When tested in freshwater, the striped bass, *Roccus saxatilis*, appeared quite sensitive, with 24-, 48- and 96-hour LC_{50} values at 31.8, 11.8 and 6.7 mg formaldehyde/ℓ (Wellborn, 1969).

The black bullhead appeared to be fairly sensitive to formaldehyde compared with other species tested (see Table 6-1), with 24- and 96-hour LC_{50} values of 69.2 and 24.8 mg/ℓ (Bills et al., 1977). The 72-hour LC_{50} values determined in black bullhead, *Ictalurus melas*, golden shiner, *Notemigonus crysoleucus*, and bluegill sunfish, *L. macrochirus*, were 17.1, 23.6 and 30.4, respectively. In the carp, *Cyprinus carpio*, green sunfish, *Lepomis cyanellus*, and tilapia, *Tilapia* sp., 72-hour LC_{50} values were >26.6, 34.2 and 38.0 mg/ℓ with no deaths occurring in any of these three species at levels up to 26.6 mg formaldehyde/ℓ (Helms, 1967). Gehm (1945) reported the minimum concentration causing death in shiners exposed at 18°C for 120 hours to be 50 mg formaldehyde/ℓ. Studies by Hinton and Eversole (1978, 1980) determined the levels of formaldehyde lethal to three stages of American eel, *Anguilla rostrata*. The 96-hour LC_{50} values in the glass, black and yellow eel stage were 31.1, 82.9 and 122.1 mg formaldehyde/ℓ, respectively. The 96-hour LC_0, LC_{50} and LC_{100} values were 30, 41 and 50 mg/ℓ in the zebrafish, *Brachydanio rerio*, and 48-hour lethal levels were

10, 22 and 25 mg/ℓ, respectively, in the golden orfe, Leuciscus idus, (Wellens, 1982). Juhnke and Luedemann (1978), conducting toxicity tests using the golden orfe, reported 48-hour LC_0, LC_{50} and LC_{100} values of 12.9 and 9.6, 32.4 and 15.0, and 39.0 and 22.8 mg/ℓ.

Toxic effects of formaldehyde on freshwater fish (trout and salmon) included changes in gill function, hypochloremia, depressed plasma calcium and carbon dioxide, reduced blood pH, and decreased oxygen consumption (Wedemeyer, 1971). Effects occurred rapidly after a 1-hour exposure at 200 mg/ℓ in rainbow trout and required ~24 hours for recovery (Wedemeyer and Yasutake, 1974). Nieminen et al. (1983) reported that formalin treatment caused increased blood hemoglobin, packed cell volume, blood glucose and plasma protein concentrations in rainbow trout and Atlantic salmon.

In the marine pompano, Trachinotus carolinus, 24-, 48- and 96-hour LC_{50} values were determined for formaldehyde at salinities of 10, 20 and 30 ppt (Birdsong and Avault, 1971). Variations in salinity did not greatly alter the lethality of formaldehyde, but pompano appeared most sensitive at higher salinities. At 30 ppt the 24-, 48- and 96-hour LC_{50} values were 78.0, 73.7 and 69.1 mg formaldehyde/ℓ.

In the freshwater crustacean, Daphnia magna, the 24-hour EC_0, EC_{50} and EC_{100} for immobilization were 11.6, 14.7 and 18.6 mg formaldehyde/ℓ (Bringmann and Kuehn, 1982). Dowden and Bennett (1965) indicated that the 24-hour LC_{50} in D. magna was between 100 and 1000 mg/ℓ. Prasad (1980) reported that the 96-hour LC_{50} values for the invertebrates, Daphnia, Bosmina and Cyclops, were all 20 mg/ℓ while Chironomid larva were more resistant (450 mg/ℓ). Bills et al. (1977) reported the 1-, 3-, 6-, 24- and 96-hour EC_{50} values for immobilization in the sand shrimp, Cypridopsis sp., to be 3.6, 2.56, 0.48, 0.46 and 0.42 mg formaldehyde/ℓ, respectively.

This species appears very sensitive compared with fish species and other aquatic invertebrates. In the fairy shrimp, Streptocephalus seali, mortality was not greatly affected after 48 hours of exposure at 25 mg/ℓ (Moss, 1978). In the freshwater prawn, Palaemonetes hadiakensis, 3-, 6-, 24- and 96-hour EC_{50} values for immobilization were 860, 760, 442 and 186 mg/ℓ. The 24- and 96-hour EC_{50} values for loss of tactile response in the backswimmer, Notonecta sp., and bivalve clam, Corbicula sp., were 1800 and 334 mg/ℓ and 320 and 50.4 mg/ℓ, respectively. In the adult Asiatic clam, Corbicula manilenais, the 24- and 96-hour LC_{50} values in static tests were 296 and 46.6 mg formaldehyde/ℓ (Chandler and Marking, 1979). The 96-hour LC_{50} determined in flow-through tests was 35.2 mg/ℓ. The 24-hour LC_{50} for the sand shrimp, Metapenaeus ensis, was 100 mg/ℓ (Tseng and Chen, 1982). The 1-, 3-, 6-, 24- and 96-hour EC_{50} values for loss of response to tactile stimuli in the snail, Helisoma sp., were 1410, 536, 312, 284 and 37.2 mg formaldehyde/ℓ, respectively (Bills et al., 1977). In the aquatic larval of the mosquito, Aedes aegypti, the 4-hour LC_{50} was 2705 mg formaldehyde/ℓ (Kramer et al., 1983).

6.2. CHRONIC EFFECTS

Helms (1967) conducted lethality tests of formaldehyde in tadpoles of two frog species and one toad. The 24-, 48- and 72-hour LC_{50} values for the leopard frog larvae, Rana pipiens, were 8.4, 8.0 and 8.0 mg formaldehyde/ℓ, with a 72-hour LC_{100} at 11.4 mg/ℓ. Tadpoles of the bullfrog, Rano catesbeiana, were more resistant, having 24-, 48- and 72-hour LC_{50} values at 20.1, 17.9 and 17.9 mg/ℓ with a 72-hour LC_{100} at 30.4 mg formaldehyde/ℓ. In the toad larvae, Bufo sp., the 72-hour LC_{50} and LC_{100} values were 17.1 and 19.0 mg/ℓ, respectively (Helms, 1967).

Carmichael (1983) exposed tadpoles of the Rio Grande leopard frog, Rana berlandieri, to formalin for 24 hours and recorded mortality data. At concentrations ≤6.0 mg formaldehyde/ℓ, no mortality occurred. At 9.2, 13.6, 20.4 and 30.5 mg formaldehyde/ℓ, mortality was 13, 35, 78 and 100%.

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978) reported the toxicity threshold levels for inhibited cell multiplication for the blue-green algae, Microcystis aeruginosa, and the green algae, Scenedesmus quadricauda. The lowest levels causing decreased cell growth, determined turbidimetrically, following 8-day incubations, were 0.137 mg/ℓ in the blue-green and 0.875 mg/ℓ in the green algae.

6.4. RESIDUE

Formaldehyde content was determined in fish, molluscs and crustaceans from the Mediterranean Sea and varied from 0-4 mg/kg in prawn, Perullus angulatus, to 11-30 mg/kg in squid, Todarodes saggittatus, (Cantoni et al., 1976). It was not specified whether these were due to contamination or were natural tissue levels.

Bills et al. (1977) reported that the toxicity of rainbow trout was comparable in solutions of formaldehyde that had been aged for 1, 2 and 3 weeks. The data suggest that formaldehyde may persist in water, but it was not specified whether these studies accounted for microbial or other degradation of the compound.

Additional data regarding the fate of formaldehyde in the aquatic environment are discussed in Chapter 2.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Kuehn (1980) reported a toxicity threshold for inhibited cell multiplication at 4.9 mg formaldehyde/ℓ in the bacteria, Pseudomonas putida, exposed for 16 hours. In the protozoan, Entosiphon sulcaturn, the toxicity threshold was 7.7 mg/ℓ following 72 hours of exposure to formaldehyde. Bulich and Isenberg (1980) reported the 5-minute EC_{50} for bioluminescence in the bacteria, Photobacterium phosphoreum, to be 3.0 mg/ℓ. Using the same test method, McFeters et al. (1983) reported a 5-minute EC_{50} at 904.17 mg/ℓ.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration has established a workplace regulation of 3 ppm formaldehyde vapor as a TWA over 8 hours. The acceptable ceiling concentration is 5 ppm, and the maximum peak concentration is 10 ppm for 30 minutes (Code of Federal Regulations, 1981). NIOSH (1976) previously recommended that employees not be exposed to formaldehyde at >1.2 mg/m^3 (1 ppm). Because of the positive carcinogenicity bioassay showing development of nasal cancer in F344 mice and B6C3F1 mice (Kerns et al., 1983a,b), NIOSH (1981) recommended that formaldehyde be handled as a potential occupational carcinogen; thus, a safe level cannot be determined. The ACGIH (1984) has recently classified formaldehyde as a suspect human carcinogen and proposed a TWA-TLV of 1 ppm (1.5 mg/m^3), with a STEL of 2 ppm (3 mg/m^3) for a 15-minute exposure.

7.2. AQUATIC

A standard of 1.0 mg formaldehyde/ℓ for sewage and industrial effluent was established in England by the Mersey River Board for the protection of aquatic organisms (McKee and Wolf, 1963).

8. RISK ASSESSMENT

Based on the available carcinogenicity data on formaldehyde following its inhalation in animals, the U.S. EPA (Federal Register, 1984) has concluded that formaldehyde is a potential carcinogen to humans. It is therefore appropriate to determine the risk of cancer in humans (q_1* value) based on these data in animals. Based on the assumption that there is no safe exposure level for carcinogenic compounds, it is inappropriate to determine an ADI level for formaldehyde.

The CIIT bioassay of formaldehyde (CIIT, 1979; Swenberg et al. 1980a,b; Kerns et al., 1983a,b) was the first study to demonstrate a carcinogenic effect in rats exposed by inhalation. In this study, groups of 120 males and 120 females of F344 rats and B6C3F1 mice were exposed to 2.0, 5.6 or 14.3 ppm formaldehyde vapor for 6 hours/day, 5 days/week for 24 months (see Section 5.1.). Squamous cell carcinoma, a very rare spontaneous tumor among these rodents, developed in 51/117 male and 52/115 female rats exposed at the 14.3 ppm (17.6 mg/m³) level. Two cases of squamous cell carcinoma, one in each sex, occurred among rats exposed at 5.6 ppm (6.9 mg/m³), indicating a dose-related response (see Table 5-1). No similar tumors were reported among rats treated at 2.0 ppm (2.5 mg/m³) or among air-exposed controls. The incidence of benign polypoid adenomas was 1/232, 8/236, 6/235 and 5/232 among groups of rats exposed at 0, 2.0, 5.6 and 14.3 ppm, respectively, which does not exhibit a strict dose-related response. The somewhat lower incidence of adenoma among the higher dose groups may have been offset by the high level of nasal proliferation and squamous cell carcinoma among rats of these groups. The U.S. EPA (Federal Register 1984) indicated that the development of benign adenomas was likely to be related to formaldehyde exposure, since these are rare spontaneous tumors and their occurrence represents a significant pathology at low doses.

The tumor response in mice was less that that observed in rats (see Table 5-1). Two cases of squamous cell carcinoma were observed among 120 male mice exposed at 14.3 ppm (17.6 mg/m³), which was not significantly ($p>0.05$) increased when compared with matched controls. These tumors, however, originated in the anterior nasal turbinates and were of the same histology as those in rats. In addition to the similarity between these tumors and those seen in rats, the U.S. EPA (Federal Register, 1984) regarded the low incidences of nasal tumors (2/120) among male mice suggestive of a carcinogenic response because of the very low spontaneous rate of nasal tumors in B6C3F1 mice.

The apparent difference in sensitivity to the carcinogenic activity of formaldehyde may result from differences in the dose of the compound reaching the nasal epithelium (Gibson, 1983b). It has been shown that mice are more sensitive to the respiratory depressant effects of formaldehyde than rats (see Section 5.6.). Mice exhibit a greater decrease in respiratory rate than rats and, therefore, are exposed to a lower dose per unit area of nasal epithelium. Barrow et al. (1983) estimated that because of the depressed respiratory rate, mice inhaled approximately half of the 15 ppm formaldehyde dose that the rats inhaled.

Data from an interim report of a lifetime inhalation study in male Sprague-Dawley rats (Albert et al., 1982), support the CIIT (1979) study in demonstrating the production of nasal squamous cell carcinoma by formaldehyde. In this study, a group of 100 male rats were exposed to formaldehyde at 14.2 ppm for 6 hours/day, 5 days/week for their lifetime (see Section

5.1.). The interim report, prepared after 588 days (382 exposures), identified nasal squamous cell carcinoma in 10 of 38 rats that died during this period. There were no similar tumors among 28 air-exposed controls (see Table 5-2). This incidence of squamous cell carcinoma was significantly ($p=0.001$) increased, and the authors expected a higher incidence among the 62 exposed survivors.

The current epidemiological data on humans do not clearly show an association between exposure to formaldehyde and increased cancer mortality. Walrath and Fraumeni (1983a,b) suggested that there was a correlation between exposure to formaldehyde and skin cancer among 1106 deceased morticians, but only 8 skin cancer deaths were reported with 3.2 expected (see Table 5-3). Marsh (1982) reported that among a group of chemical plant workers who were exposed to formaldehyde for ≤ 5 years and allowed 20 years latency, 5 digestive tract cancers occurred with 1.56 expected ($p<0.01$) (see Table 5-4). Acheson et al. (1984) conducted a mortality study of 1619 deaths among 7680 chemical factory workers. The observed number of deaths from nasal, lung, buccal and pharyngeal, or laryngeal cancer was not different from expected numbers. Classification by level of formaldehyde exposure and length of service did not show an association between extent of exposure and lung cancer (see Table 5-5). Other available epidemiological studies (see Section 5.1.) failed to show an increase in observed cancers versus expected, or suffer from inherent problems such as a small number of cancer deaths or complex chemical exposures.

Based on their assessment of levels of formaldehyde in residential homes and exposure of garment workers, the Office of Toxic Substances (OTS) has developed a preliminary quantitative estimate of the carcinogenic risk associated with inhalation exposure to formaldehyde (U.S. EPA, 1985). The question of formaldehyde's carcinogenic potential by ingestion has not been assessed as yet by the U.S. EPA. The U.S. EPA Carcinogen Assessment Group (CAG) has classified this chemical as "probably" carcinogenic in humans, however qualitative estimates of the cancer risk associated with formaldehyde exposure will be evaluated at a later date.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

A number of studies are available that are useful in assessing the chronic toxicity of formaldehyde in experimental animals (see Section 5.5.). Data are sufficient to determine human MEDs, CSs and RQs from the inhalation studies by Horton et al. (1963), Fel'dman and Bonashevskaya (1971), Kerns et al. (1983a,b), Dalbey (1982) and Rusch et al. (1983a,b). The animal exposure levels and toxic effects relevant to the derivation of RQ values for each study are summarized in Table 9-1. The human MEDs have been determined based on the assumption that animals and humans absorb equivalent doses on a body weight basis (mg/kg/day). Intermittent exposures were expanded to equivalent continuous exposure. The MEDs determined from subchronic animal exposures were corrected to approximate chronic exposure using an uncertainty factor of 10.

A review of the CSs for chronic exposure to formaldehyde (see Table 9-1) shows that all scores, determined from several studies in several species, fall within the narrow range of 33-43. Selection of the most appropriate data to represent the chronic toxicity of formaldehyde is based on the quality of the study, its duration of exposure and the resultant CS. The inhalation study in rats conducted by Kerns et al. (1983a,b) used several dose levels with controls, long duration and complete histopathological examination; therefore, it is deemed the most appropriate representation of chronic formaldehyde toxicity. Rats exposed at 2.0 ppm (2.46 mg/m^3) for 6 hours/day, 5 days/week for 24 months developed squamous cell metaplasia of the anterior nasal turbinates with micropurulent rhinitis. Treatment at 5.6 ppm (6.88 mg/m^3) on the same regimen produced slightly more severe nasal cytotoxic effects and increased mortality. The high dose level, resulting

TABLE 9-1

Composite Scores for the Inhalation Toxicity of Formaldehyde

Species	Animal Exposure	Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Mice	50 mg/m^3 1 hour/day, 3 days/week x 35 weeks	0.64[a]	5.8	Histopathologic changes in tracheobronchial epithelium (basal-cell hyperplasia, stratification); tracheobronchitis	7	41	10	Horton et al., 1963
Mice	100 mg/m^3 1 hour/day, 3 days/week x 35 weeks	1.27[a]	5.3	Histopathologic changes in tracheobronchial epithelium (basal-cell hyperplasia, stratification, squamous cell metaplasia); tracheobronchitis	8	43	10	Horton et al., 1963
Mice	50 mg/m^3 TWA 1 hour/day, 3 days/week x 35 weeks followed by 150 mg/m^3 for remainder of lifetime	12.71[b]	3.8	More severe tracheobronchial changes than above; all died by the 69th week of exposure	10	38	100	Horton et al., 1963
Mice	6.88 mg/m^3 6 hours/day, 5 days/week x 24 months	8.64	4.1	Squamous cell hyperplasia of nasal turbinates	8	33	100	Kerns et al., 1983a,b
Rats	2.46 mg/m^3 6 hours/day, 5 days/week x 24 months	3.36	4.7	Mucopurulent rhinitis, epithelial dysplasia and squamous metaplasia of of nasal cavity	8	38	100	Kerns et al., 1983a,b
Rats	6.88 mg/m^3 6 hours/day, 5 day/week x 24 months	9.41	4.1	Mucopurulent rhinitis, epithelial dysplasia and squamous metaplasia of of nasal cavity; increased mortality after 12 months	10	41	10	Kerns et al., 1983a,b
Rats	1.0 mg/m^3 24 hours/day 7 days/week x 3 months	0.77[a]	5.7	Slight pulmonary inflammation; histological changes in liver including nuclear polymorphism, focal hyperplasia, activation of reticuloendothial system elements; dilated vessels in the juxtamedullary zone of the renal cortex; focal proliferation of the glial elements of the parietal area in the cerebral cortex	7	40	100	Fel'dman and Bonashevskaya, 1971
Rats	3.6 mg/m^3 22 hours/day, 7 days/week x 26 weeks	2.53[a]	4.9	Squamous cell metaplasia, basal cell hyperplasia in nasal turbinates; decreased liver and body weights	8	39	100	Rusch et al., 1983a,b

TABLE 9-1 (cont.)

Species	Animal Exposure	Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Hamsters	12.3 mg/m³ 5 hours/ day, 5 days/week x lifetime	14.5	3.8	Minimal increase in hyperplasia and metaplasia of nasal epithelium; decrease in survival	10	38	100	Dalbey, 1982
Monkeys	3.6 mg/m³ 22 hours/ day, 7 days/week x 26 weeks	7.55[a]	4.2	Squamous cell metaplasia of nasal turbinates	8	33	100	Rusch et al., 1983a,b

[a] The MED was divided by 10 to convert to chronic exposure.

[b] Assuming the TWA concentration was 100 mg/m³

in a human MED of 9.41 mg/day, a CS of 41 and an RQ of 10, is selected as most appropriate to represent the chronic toxicity of formaldehyde (Table 9-2).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR FOR CARCINOGENICITY

The carcinogenicity bioassays of formaldehyde clearly demonstrate a carcinogenic effect in the nasal cavity in rats and evidence in mice is strongly suggestive (Kerns et al., 1983a,b; Albert et al., 1982). Studies have shown that formaldehyde induces a high level of nasal squamous cell carcinoma in male and female F344 rats (Kerns et al., 1983a,b) and male Sprague-Dawley rats (Albert et al., 1982) following chronic exposure at 14.2-14.3 ppm (6 hours/day, 5 days/week) (see Tables 5-1 and 5-2). Kerns et al. (1983a,b) also reported two nasal squamous cell carcinomas in male mice (2/120) exposed at 14.3 ppm. This incidence was not significantly increased compared with controls (0/120), but the very low spontaneous incidence of this tumor type among untreated rodents led the U.S. EPA (Federal Register, 1984) to regard the two cases of carcinoma indicative of a carcinogenic effect. Supportive of the carcinogenicity of formaldehyde, preneoplastic cytopathologies have been demonstrated in mice and other laboratory animals following chronic, subchronic and acute exposures (see Sections 5.5. and 5.6.). Mutagenicity data on formaldehyde are both positive and negative, with mutagenic and genotoxic effects shown in cultured human cells but no clearly positive mutagenesis in in vivo mammalian tests (see Section 5.2. and Table 5-6).

Evidence of the carcinogenicity of formaldehyde in humans is not conclusive. Many studies show no increase in the risk of cancer among exposed groups compared with control populations. Other studies lack sufficient numbers of cancer deaths or do not implicate formaldehyde clearly enough to

TABLE 9-2

Formaldehyde

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	9.41 mg/day
Effect:	squamous cell metaplasia, mucopurulent rhinitis, epithelial dyspasia of the nasal turbinates and increased mortality
Reference:	Kerns et al., 1983a,b
RV_d:	4.1
RV_e:	10
Composite Score:	41
RQ:	10

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*Equivalent human dose

demonstrate a conclusive carcinogenic effect. Walrath and Fraumeni (1983a,b) suggested a correlation between skin cancer and formaldehyde exposure among 1106 deceased morticians, based upon 8 skin cancer deaths (3.2 expected) (see Table 5-3). Marsh (1982) suggested an increase in digestive tract cancers among formaldehyde-exposed chemical plant workers, with 5 cases observed and 1.56 expected (see Table 5-4).

Based on the positive evidence of carcinogenicity of formaldehyde in rodents and the lack of confirming data in exposed humans, formaldehyde is most appropriately classified as a Group 2B chemical according to the IARC classification scheme. According to the Guidelines for Carcinogen Risk Assessment established by the Carcinogen Assessment Group (Federal Register, 1984b), formaldehyde would be classified as group B2 chemical which means that formaldehyde is "probably" carcinogenic t humans.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December and January, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, the following documents were obtained and reviewed:

U.S. EPA. 1983. Deliberations of the Consensus Workshop on Formaldehyde held October 3-6, 1983. Little Rock, AR.

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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